

**THE USE AND USEFULNESS OF ANTIDEPRESSANTS A
TECHNICAL REVIEW OF EVIDENCE BY A TASK FORCE OF THE CINP**

Members of the Task Force:

Norman Sartorius (Chairperson), Thomas C. Baghai, David Stewart Baldwin, Ursula Brand, W. Wolfgang Fleischhacker, Guy Goodwin, Heinz Grunze, Martin Knapp, Brian E. Leonard, Jeffrey Lieberman, Yoshibumi Nakane, Roger M. Pinder, Alan F. Schatzberg, Jaromír Švestka

This text has been written by Thomas C. Baghai, Heinz Grunze and Norman Sartorius, David S. Baldwin, Barbara Barrett, Guy Goodwin, Kareem Ghalib, Martin Knapp, Brian E. Leonard, John C. Markowitz, Frank Padberg and Roger Pinder

and edited by Thomas C. Baghai, Heinz Grunze and Norman Sartorius

Specific comments and contributions to some of the chapters have been contributed by Max Fink, Robin Jacoby, Peter Jensen, Anita Riecher-Rössler.

The names of the persons who have produced the first draft of the chapters are given in the table of contents.

Correspondence to:

Norman Sartorius, MD, PhD, Chairperson of CINP Task Force
14, chemin Colladon, 1209 Geneva, Switzerland
Phone: +41-22- 788 23 31
Fax: +41-22-788 23 34
E-mail: mail@normansartorius.com

with copy to:

Thomas C. Baghai, MD
Dpt. of Psychiatry and Psychotherapy
Ludwig-Maximilians-University Munich
Nussbaumstr. 7, D-80336 Munich
Germany
Phone: +49-89-5160-5731
Fax: +49-89-5160-5738
E-mail: Baghai@med.uni-muenchen.de

Heinz Grunze, MD
Dpt. of Psychiatry and Psychotherapy
Ludwig-Maximilians-University Munich
Nussbaumstr. 7, D-80336 Munich
Germany
Phone: +49-89-5160-5335
Fax: +49-89-5160-5330
E-mail: Heinz.Grunze@med.uni-muenchen.de

Contents

THE USE AND USEFULNESS OF ANTIDEPRESSANTS A TECHNICAL REVIEW OF EVIDENCE BY A

TASK FORCE OF THE CINP	1
1 Foreword	5
2 Editorial introduction	6
3 Introduction	7
4 Health Economics - the Cost of illness	13
4.1 Background	13
4.2 The broad costs of depression	14
4.3 Methodology-Economic evaluation	17
4.4 Economic evidence for pharmacological treatment options	21
4.5 Evidence on the cost-effectiveness of antidepressants and care management	28
4.6 Economic evidence for pharmacological treatment options	29
4.7 Implications – economic evidence for pharmacological treatment options	30
4.8 Economic evidence for psychological treatment options	32
5 Diagnosis and Epidemiology	35
5.1 Diagnosis of depressive disorders	35
5.2 Specific features of manifestations of depressive syndromes	38
5.3 Epidemiology of depressive disorders	51
6 Methodology	53
6.1 Consensus process	53
6.2 Data Source	54
6.3 Limitation	55
7 Standard of care	57
7.1 Diagnosis	57
7.2 Access to Mental Health Services	60
7.3 Enhanced care	61
8 Goals of treatment - response, remission, recovery	63
8.1 Acute treatment	64
8.2 Continuation treatment	69
8.3 Maintenance treatment	70
8.4 Management of side effects	72
9 Specific age and gender related conditions	73
9.1 Gender related differences	73
9.2 Age related differences	77
10 Mechanisms of action of antidepressants	100
10.1 The development of antidepressants based on the monoamine hypothesis of depression..	100
10.2 New developments leading to a new understanding of the mechanism of action of antidepressants	104
10.3 The role of pharmacogenetics in the understanding of how antidepressants work	111
11 Pharmacological acute phase treatment options	114
11.1 Introduction and general information about antidepressants	114
11.2 Summary of side effects	122
11.3 Selective serotonin reuptake inhibitors (SSRI)	130
11.4 Selective serotonin and noradrenaline reuptake inhibitors (SNRI)	133
11.5 Selective noradrenaline reuptake inhibitors (NARI)	135

11.6	Monoaminoxidase inhibitors (MAOI, MAOBI, RIMA)	136
11.7	α_2 -receptor blocking tetracyclic antidepressants	138
11.8	Serotonin modulating antidepressants (SMA)	139
11.9	Dopamine and noradrenaline reuptake inhibitors (DNRI)	141
11.10	Tri- and tetracyclic antidepressants (TCA)	142
11.11	Combination treatment	144
11.12	Herbal antidepressants	147
11.13	Q-3 polyunsaturated fatty acids	149
11.14	Augmentation strategies	150
11.15	New developments and novel pharmacological treatment approaches	162
12	Pharmacological maintenance therapy	168
12.1	Continuation treatment	168
12.2	Prophylactic treatment	169
13	Suicidality and antidepressants	174
14	Antidepressant drugs in the treatment of anxiety disorders	178
14.1	Generalized Anxiety Disorder	178
14.2	Panic disorder	179
14.3	Social phobia	179
14.4	Post-traumatic stress disorder	180
14.5	Obsessive-compulsive disorder	180
15	Other treatments	182
15.1	Psychotherapy	182
15.2	Electroconvulsive Therapy (ECT)	183
15.3	Recently developed and other non-pharmacological treatments	190
16	Conclusions and Implications	199
17	References	200
18	Annexes	266
18.1	Annex 1 - Additional information on the types of economic evaluation	266
18.2	Annex 2 - Additional information on Electroconvulsive Therapy	272
18.3	Annex 3 - Additional information on transcranial magnetic stimulation	285
18.4	Annex 4 - Additional information on vagus nerve stimulation (VNS)	289
18.5	Annex 5 - Additional information on Acupuncture	292
18.6	Annex 6 - Additional information on Psychotherapy	294

1 **Disclosure remarks**

Placeholder

Detailed disclosure remarks will follow in the final
version of the document.

1 Foreword

Placeholder

Foreword of Professor Leonard, President of the CINP will follow in the final version of the document.

2 Editorial introduction

Dear colleagues,

recently the necessity of the treatment of depressions, especially the use of antidepressants, have become a public agenda. The ongoing discussion, however, seems to be mainly based on beliefs and opinions, partly also misinformation or a lack of information. In order to allow a fair and evidence-based discussion on the use of antidepressants the CINP Task Force compiled this technical review entitled “The use and usefulness of antidepressants”. It is meant both as the scientific basis for a future consensus statement of the CINP about this topic, as well as a comprehensive review of the existing evidence, compiled and commented by experts in the field. In order to allow the busy reader quick referencing we want to briefly introduce you to the structure and content of this technical review.

The first six chapters are dedicated to the epidemiology and diagnosis of depression including socio-economic aspects, overall principles of care and treatment goals. In Chapter 6 it also details the methodology how this review has been developed. The main body of the text starting from Chapter 10 is then dedicated to the different aspects of the use of antidepressants: their mechanism of action, the effectiveness and side effect profile of each antidepressant based on the available literature from clinical studies and meta-analysis, the role of combination and augmentation strategies including other pharmacological options, and principles of continuation and prophylactic treatment. The reader will find comprehensive information on these topics for all major antidepressants, divided in chapters according to their main mechanism of action.

However, the CINP Task Force has also to acknowledge that modern treatment of depression cannot only be based on the use of pharmacological treatment strategies. The role of other treatments, most importantly psychotherapy and ECT, but also other new treatment options are briefly reviewed in Chapter 13 and, for more detailed information, in the different annexes.

On behalf of the CINP Task Force, we hope that this technical review will be an informative source of information and at the same time remains a vivid document, regularly updated and integrating new evidence when available.

Geneva, May 2006 for the CINP Task Force. N.

Sartorius, T.C. Baghai, H. Grunze

3 Introduction

The criteria that are used to assess whether a health problem is of public health importance (and therefore has priority for the health services) include the prevalence of the problem, the severity of its consequences, the likelihood that the problem will remain stable or grow if unattended and the availability of effective means of intervention to resolve or significantly reduce the problem.

Depressive disorders satisfied the first three criteria long ago. Depressive disorders are among the most frequent mental disorders and their prevalence matches that of most severe physical illnesses. The consequences of depression if left untreated are grave and include premature morbidity from various physical illnesses, disability that is more serious than that produced by frequent chronic disorders such as diabetes and chronic collagenoses. The reports of the World Health organization (WHO) indicate that depressive disorders are among the disorders that produce most significant losses of years of life due to illness and disability. Depressive disorders also significantly increase the risk of suicide and of suicidal attempts. There is high probability that the depressive disorders will become even more prevalent in the decades to come, for a variety of reasons including the increased life expectancy of the general population in many countries (resulting in an increase of the population groups that are at particularly high risks for depressive disorders), the increased life expectancy of people with chronic physical illness often accompanied by depressive disorders (e.g. chronic gastrointestinal disorders, cardiovascular disorders and stroke) the increased numbers of iatrogenic mental disorders including depression and, in both developed and developing countries, the continuously increasing levels of stress parallel to the weakening of social support. The WHO predicted that unipolar depression alone will be the second most important producer of disability by the year 2020, not only in Europe and northern America but worldwide.

The fourth criterion for public health importance and for consequent action is the availability of an effective intervention that can reduce or eliminate the problem and is suitable for widespread application. Until recently that criterion has not been satisfied for the majority of mental disorders: although public health authorities had major successes in the prevention of some mental disorders (e.g. of cretinism in areas in which the iodine deficiency has been successfully eliminated and of progressive paralysis in areas where the infection with syphilis was brought down to minimal levels) the treatment of mental disorders was, by and large, not very effective. Electroconvulsive treatment (ECT) had good effects in the treatment of people with certain forms of depressive disorders and schizophrenia but the number of those who could not benefit from ECT vastly surpassed the numbers of those who could so that that intervention did not fit the criterion of wide applicability. Psychotherapy helped many but the numbers of experts qualified to apply it were – and still are – small in most parts of the world and the psychotherapeutic techniques have only recently become sufficiently well defined to become a candidate for a subject in undergraduate medical education and in in-service training of non-psychiatrists.

The introduction of antidepressant medications changed the public health importance of depressive disorders and the priority which they had health care services. In addition to the recognition that depressive disorders are frequent and severe, that they are likely to grow in numbers in the years to come and that they are complicating the treatment of many physical disorders it gradually became evident that antidepressant medications can help a significant proportion of people with depressive disorders even when applied by general medical staff in primary care and non-psychiatric health services. It became possible to speak about one's depression because it had become accepted that depression was a disease that could be effectively treated by medical means – medications – like many other diseases. The lessened stigma of depression and the growing conviction that antidepressant medications can help made patients seek help from health workers and encouraged non-psychiatrists to

accept to deal with depression, to prescribe antidepressants and in general to see patients with depression as having a problem that can be handled by health services. The numbers of patients and doctors who thought that way grew over time supported also with the increase of the variety and numbers of medications and the encouraging descriptions of their effectiveness and ever milder side-effects. The general public and the media supported this notion as well. The Prime Minister of Norway took a few weeks off to treat his depression and came back in good health. Famous artists and other stars described their depression and the way in which they got better. Psychiatric epidemiologists published studies showing that lifetime prevalence of depressive disorders was nearly eighty percent; a figure which can be easily interpreted by the lay public as indicating that depressive disorders are part of normal life. While this change of public opinion – from seeing depressive disorders as a form of madness that medicine could not cure to being a physical illness that could be treated by pills prescribed by the general practitioner (or even just a temporary lack of energy and joyfulness that could be easily repaired) – was positive in the sense that it encouraged the patients to come forward and stimulated medical staff to learn how to deal with the disease. But, this change of opinions that came into existence in part spontaneously and in part promoted by various sects and anti-psychiatric movements also had the negative consequence of banalizing depressive disorders. Depressive disorders, it was increasingly felt were most often not really diseases: rather they were conditions that everyone had. The medications that were hailed as miraculous cure were no better than placebo. Worse: they changed people's personality and made them dependent on drugs. It was only the coalition between doctors and the producers of medications that kept alive the myth of depressive illness and its treatment with medications.

The results of studies showing that a successful treatment of depressive disorders not only helps people who suffer from them but also brings a benefit to their society and their family were not widely known nor made sufficiently public: what was much better known was that

the cost of medications was high and that the producers and distributors of medications made a lot of money. To an extent the notion that medications used for the treatment of mental disorders are expensive stems from the stigma that accompanies mental disorder and the low value that is given to people who have this disorders. Even when medications used in psychiatry are of a very low cost – the cost of a monthly supply of medications of a medication such as chlorpromazine is no more than one US \$ - governments does not buy them and the general public accepts that even one dollar per month is too much to spend for a person who in the eyes of most of the population not worth it.

At the same time, research and technological developments resulted in an increase of the number of active substances that could be used in the treatment of depression while the knowledge about the mechanisms of their action continued to grow. Results of studies carried out to assess the effectiveness of the new substances usually show that they are at least as good as the previously used medications and that they have some advantages that other drugs do not have. Studies comparing medications have grown in numbers and seem to be reaching many contradictory results. There are still far too few investigation of the effects of new medications for patients in populations outside the highly industrialized countries¹. Some studies did show differences in dosage and effects of medications given to patients living in countries with a different climate, different nutrition and different general morbidity patterns but by large there are still far too few studies that would allow definitive answers about effects of drugs on patients from different populations. The scarcity of studies on psychotropic drugs in the third world is part of the larger problem of predominance of research in a few highly developed countries. In a recent study it was shown that only 6% of the mental health publications in the scientific literature comes from other than high income

¹ More recently some of the studies sponsored by international pharmaceutical companies have included patients from India and some other countries in the third world; the results of these investigations usually do not report results obtained in such countries separately and mix the data from those countries with the rest obtained in other countries.

countries; USA and UK alone contributed 50% of the accessible scientific literature on mental health matters (Saxena et al., 2006).

In the light of these considerations it is not surprising that the CINP felt that it would be useful to carry out a detailed technical review of the uses and usefulness of antidepressant medications. The review relies on published evidence: it however also incorporates the advice and comments of leading experts in the field of psychiatry, pharmacology and public health. The review has been submitted for discussion and comments to experts including those of regulatory agencies, to patient and family organizations and to representatives of pharmaceutical industry and public health authorities. It was hoped that the combination of the review of literature with the outcome of a wide ranging discussion involving also those whose experience does not get published (or gets published in places that are difficult to access) might produce a solid basis of facts on which the CINP could then reach a consensus on the matter and made its opinion widely known. In particular the consensus was to provide a clear answer to at least the following questions:

- are antidepressant medications effective in alleviating symptoms of depression and in preventing relapses of the depressive illness?
- are the side effects of antidepressant medications that are currently in use so severe that they outweigh the benefits that these drugs can give?
- is the treatment of depressive disorders with antidepressant medications cost/effective for individuals and societies?
- what areas of scientific investigation related to antidepressant medications and their use deserve priority?
- are there depressive disorders that do not require treatment with antidepressant medications?

The Review presented here presents the evidence and summary of experience that should help to answer these questions and facilitate the process of reaching a consensus that will guide

public health action and the education of health workers, of the general public and of those who suffer from depressive illnesses.

4 Health Economics - the Cost of illness

4.1 Background

The primary and central objectives of mental health services are the alleviation of symptoms and the promotion of quality of life. However, it is also widely recognized that economic considerations need to be taken into account. One reason is the widespread recognition that the costs of mental health problems can be substantial, and that they fall widely: on those who are ill, their families, the health care system, other service systems and the wider national economy. A second reason for paying more attention to economic issues is the apparently growing cost of treatment. Some of the newer modes of treatment for mental health problems – including the newer medications for depression – are marketed at higher prices than the older treatments they could potentially replace. This has raised questions as to whether the newer treatments are cost-effective. Third, in many countries there is a better understanding of the interconnections between mental health problems, employment and social exclusion (and of the potential for effective treatments to have impacts across many life domains), and hence growing mental health interest among ministries responsible for employment and finance. But the fundamental, pervasive, durable and most important reason for being interested in the economics of depression is because the professional, pharmaceutical and other resources required to provide treatment and support are not enough to meet all needs. Scarcity is a permanent feature of all health systems, indeed of all societies. In the face of such scarcity, choices have to be made between alternative uses of the same resource or service. Economics – and, in particular, economic evaluation - aims to provide decision makers with data that can inform and assist their decisions as to how to allocate available resources.

4.2 The broad costs of depression

The cost of depression on a society is usually measured in a 'cost-of-illness study', which estimates the value of resources incurred as a result of an illness. The economic cost of an illness or condition is driven by a number of factors:

- prevalence,
- treatment and service support rates, and
- effects of the illness on ability to work.

The costs measured in a cost-of-illness study are therefore usually separated into direct and indirect costs. Direct costs include the costs of treating the illness; in the case of depression these would include the cost of primary and secondary care contacts and the cost of antidepressant medication. Indirect costs include the economic impact of premature mortality (estimated in terms of lost productivity from lost life years) and the lost productivity from economic inactivity (non-availability for work), absenteeism (days taken off work as a result of depression) and presenteeism (time at work with reduced productivity). The output of a cost-of-illness study is expressed in monetary terms and is an estimate of the total burden of a particular disease to society. Such estimates are helpful but they are not evaluative – they tell us nothing about whether treatment is needed or which treatment is most cost-effective. There have been numerous cost-of-illness studies for depression. Here we summarize just a few to illustrate the main economic impacts of the illness.

- In England, unipolar depression was estimated to cost over £9000 million in 2000, of which only £370 million were direct treatment costs. The largest cost element was productivity losses: over one year, there were 109.7 million working days lost and 2615 deaths due to depression (Thomas et al., 2003). Depression is a substantial financial burden compared with coronary heart disease, the leading single cause of death in the UK, which had an estimated economic burden of around £7000 million in 1999 (Liu et al., 2002).

- The cost of affective disorders (including both bipolar depression and unipolar depression) in the 25 countries of the European Union plus Iceland, Norway and Switzerland were modelled by Andlin-Sobocki and colleagues (Andlin-Sobocki et al., 2005) and estimated at €10566 million in 2004.
- The cost of depression in the Asia Pacific region has also been examined. (Hu, 2004) reviewed existing evidence and reported that the total cost of depression in Australia was US\$1800 million in 1997, of which 22% were direct treatment costs, and in Taiwan was US\$1400 million in 1994, of which a quarter were direct treatment costs. Another study by Hu et al, estimating the cost of depression in China, is in the process of publication.
- The economic burden of depression in the US was relatively stable between 1990 and 2000, despite an increase in the proportion of sufferers receiving treatment. The total cost in 2000 was US\$8310 million, of which almost a third was in direct medical treatment costs (Greenberg et al., 2003). The burden of depression appears to be less than the economic cost of diabetes in the US, estimated at \$13200 million in 2001 (American Diabetes Association, 2003).

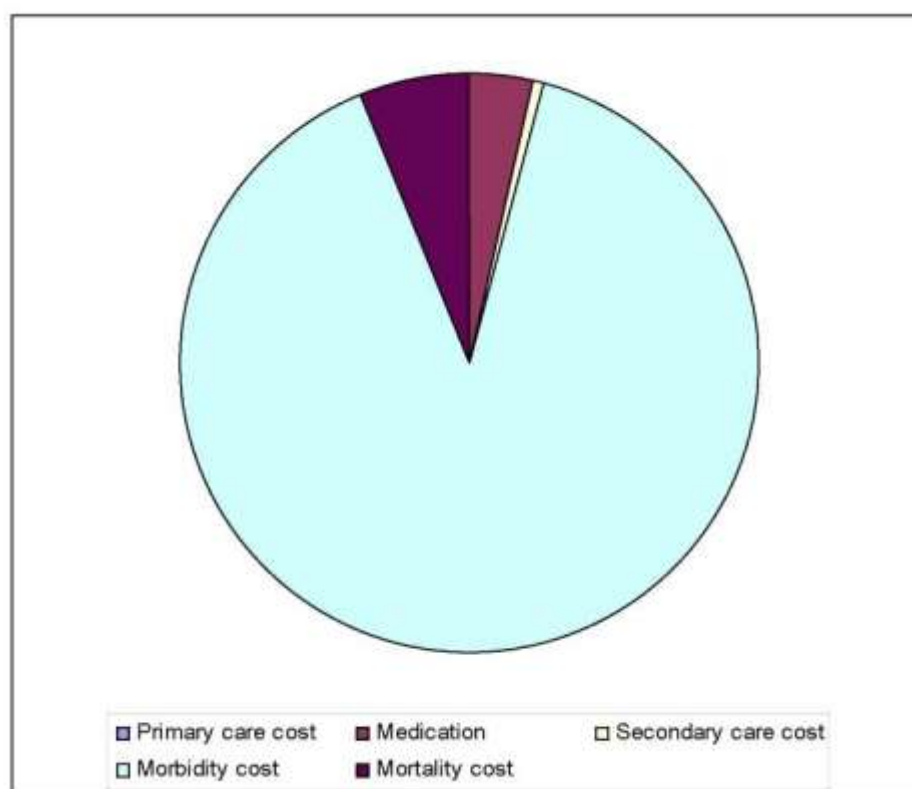
The cost-of-illness literature thus reminds us that depression not only places a financial burden on health and social services, but also on the broader economy from days lost from work and productivity losses more generally. Moreover the impact of depression on work – days absent and reduced effectiveness – will have income and career advancement implications for the individuals with the illness. Less readily measured – certainly not easily expressed in monetary terms – but of considerable importance are the affects of depression on family role and social role performance (Brown et al., 1978).

It is therefore important that evaluations of costs and outcomes take a wide cost perspective that includes not only health service costs, and social and non-statutory service costs, but also losses to the economy and to the individual and family. For example, the direct cost of

depression in England (Thomas et al., 2003) included the cost of hospital contacts, general practice consultations, drug consumption, while indirect costs included morbidity costs measured in terms of absenteeism and mortality costs in terms of the number of deaths due to suicide. Private costs to family and carers were excluded in this study. These costs are summarized in Figure 1. Clearly a relatively small proportion of total costs fall on direct treatment costs and the cost of the drug, total costs are driven by the ability of patients to return to work (morbidity costs). However, we shall see that analyses including morbidity and mortality costs are relatively rare. Instead most economic evaluations have tended to take a health systems approach, only including costs to primary and secondary care and medication.

Figure 1

The costs of depression in England, 2000 from (Thomas et al., 2003)



The need for this wider perspective is illustrated by Simon et al (Simon et al., 2000a), who reported secondary analyses of an RCT of an SSRI. They found that patients across both arms (SSRI and TCA) whose symptoms had improved twelve months after the start of the trial

were more likely to continue in paid employment (if working at baseline) or to return to work (if not originally employed) compared to patients whose symptoms had not changed. Clinical improvement was also associated with fewer work days lost through illness, but not with the typical number of hours worked per week. For people whose symptoms improved there was a marginally significant reduction in health care costs, although not until the second year after initiating antidepressant treatment. The impact on employment was therefore both larger and more immediate than the impact on health service costs. Another study shows that the impact of symptom alleviation on workplace performance can be rapid (Berndt et al., 1998). At-work performance in this US study improved for chronically depressed people as the severity of their symptoms reduced. Over two-thirds of the observed improvement in work performance was found to have occurred in the first four weeks after initiating treatment with an antidepressant. In Canada, Dewa et al (Dewa et al., 2003) found that the use of recommended antidepressants at recommended doses improved symptoms and in turn improved employment outcomes for a large sample of workers. Similarly, the large-sample, six-country LIDO study found that patients with improved depression symptoms had less absenteeism (Simon et al., 2002). These employment changes are all the more significant in the face of ending stigma and discrimination by employers against people with mental health problems (McDaid et al., 2005).

4.3 Methodology-Economic evaluation²

4.3.1 Core questions

Decision makers face two central questions when considering whether to use or recommend a particular treatment for depression. The first is the clinical question, which asks whether an antidepressant is effective in improving patient health, or – when considering two or more

² See chapter 18.1 for more detailed information in Annex 1 - Additional information on the types of economic evaluation

treatment options – which of them has the better or best outcomes. Once the decision maker knows that a particular treatment is effective, s/he wants an answer to the second question: is it cost-effective? That is, does the treatment achieve the improved outcomes or quality of life at a cost that is worth paying?

These two questions (Is the treatment effective? Is it worth it?) sit at the heart of cost-effectiveness analysis. While it is always going to be necessary to reformulate these questions in ways that make them answerable with empirical research, their simplicity should never be forgotten. However, providing answers to these questions is obviously nothing like as simple. It must also be emphasized that cost-effectiveness analysis does what its name suggests: it looks at both costs and effectiveness (outcomes). So, comparing the costs of one treatment with another, without any evidence on outcomes, does not constitute an economic evaluation. Such an exercise might be a helpful description of service utilization patterns and associated costs, as we have just seen in looking at the cost-of-illness evidence, but it does not provide enough information to assist service professionals, managers or others facing the choice between two or more alternatives. Similarly, calculating the costs and outcomes of a single service could be interesting but cannot be classed as an economic evaluation unless those costs and outcomes are compared with equivalent data for another service, or even compared with the option of ‘doing nothing’, and so again the study cannot tell us whether the service is worth providing. Uncontrolled mirror design studies often run into this problem. It is important to emphasize – as we shall note again below – that an intervention’s cost-effectiveness is relative to the comparator in the evaluation, which makes the choice of comparator crucial.

4.3.2 Types of economic evaluation

There are a number of different modes of economic evaluation, each with their associated data needs, advantages, disadvantages and uses. Good accounts of health economic evaluation

methods (although with very few mental health examples) are given by Drummond et al (Drummond et al., 2005) and Drummond & McGuire (Drummond et al., 2001). The methods used in health economic evaluations are developing quite rapidly and consequently some of the techniques mentioned later in this report have been in use in empirical studies for only a short time.

A detailed account of the methods for economic evaluation is given in appendix X. In brief, cost-effectiveness analysis combines costs with a single disease-specific outcome measure such as a depression symptom scale. The incremental cost-effectiveness ratio (ICER) is computed as the difference in cost between the two treatments divided by the difference in outcomes. In a cost-utility analysis, effectiveness is reduced to a single outcome index of utility such as the quality adjusted life year (QALY) or disability adjusted life year (DALY). Incremental cost-utility ratios can thus be calculated and compared over different conditions and disease areas, allowing strategic decision makers in a health system to judge whether resources are most effectively deployed in say, treating depression or treating breast cancer. Cost-benefit analysis generates monetary valuations of outcomes to compare costs and benefits directly, which in principal opens up a wider set of comparisons for decision makers, including non-health care options. In cost-consequence analysis, costs are reported alongside a range of outcome measures in an attempt to capture the broader picture of the impact of the intervention. Finally, cost-minimization analysis involves assessment of costs only, given the already established equality of outcomes. A summary of methods for economic evaluation is given in Table 1.

1 **Table 1**

2 Methods for economic evaluation

Type of analysis	Outcome	Advantages	Disadvantages
Cost-effectiveness	Disease-specific outcome such as depression scale	Meaningful and understandable analysis	Can not compare across diseases
Cost-utility	Single outcome such as QALY or DALY	Can compare across diseases	Not suitable in all disease areas particularly mental health because of difficulties of utility measurement
Cost-benefit	Monetary	Understandable and simple analysis	Difficult to convert health outcomes into monetary terms
Cost-consequence	Specific range of disease- and other	Includes range of outcomes in analysis	Difficult to draw firm conclusions if outcomes move in different directions
Cost-minimization	Outcomes must be the equal	Understandable and simple analysis	Can rarely be used because outcomes are rarely known with certainty to be equal.

4.3.3 Search strategy

We carried out a systematic review, searching on MEDLINE, EMBASE and PsychInfo for the period January 1985 to November 2005. The search was restricted to articles with the key words ‘depression’ or ‘depressive disorder’ and ‘cost and cost analysis’, or ‘cost-effectiveness’, or ‘economic’. Following the search of the databases, a hand-search of the references of included articles was undertaken to identify any relevant studies. Information on the articles was recorded using a structured pro forma and included consideration of the following inclusion criteria:

- Focus on adults with depression
- Comparative analysis of alternative interventions

- Undertaken within a randomized controlled trial (RCT), non-random comparison or modeling study
- Considered the cost-effectiveness of antidepressants, or of care or case management when in combination with, or compared to antidepressants or of physical treatments.
- Includes the systematic assessment of both costs and outcomes, including cost-effectiveness, cost-utility, cost-benefit, cost-consequence and cost-minimization analysis

4.4 Economic evidence for pharmacological treatment options

The literature search retrieved almost 3000 references, although only 50 are included in the final review. Papers were excluded because they did not focus on depression, they did not include costs or they did not compare two or more alternative interventions. The relative cost-effectiveness of antidepressants is determined by a number of factors, most importantly the relative efficacy. The SSRIs and other newer antidepressants have a considerably higher purchase price than the TCAs, and higher drug costs can lead to higher total costs. However it is unclear how long this trend will continue as many of the SSRIs and newer antidepressants are now coming off patent and in many countries (though not all) are then sold generically at a lower price: for example, in March 2000 a 30-day supply of fluoxetine (Prozac) in the UK cost £19.34 but by March 2005 the equivalent generic fluoxetine price was £2.11. Cost-effectiveness is also influenced by patient adherence. Adherence is generally low and dropout rates high among individuals commencing antidepressant treatment, which impacts on the effectiveness of the drug. One explanation for poor adherence is the unpleasant side effects associated with the drugs; these include as dry mouth, sedation and blurred vision. If the SSRIs and the other newer antidepressants have better side-effect profiles than the TCAs, the newer preparations may improve adherence and outcomes and thus also improve cost-effectiveness.

4.4.1 Selective serotonin reuptake inhibitors (SSRIs)

We identified 32 papers that appraised the cost-effectiveness of SSRIs for depression, though only seven used data from prospective trials or naturalistic settings, with the remaining evidence coming from ‘models’.

Simon and colleagues (Simon et al., 1996; Simon et al., 1999a) carried out a prospective, naturalistic, randomized trial with economic evaluation comparing alternative antidepressant therapies. Patients attending primary care clinics in the US and initiating antidepressant treatment were randomized to fluoxetine (an SSRI) or desipramine or imipramine (TCAs). In the short-term (six-months) treatment dropout was lower, there were fewer adverse effects, and achievement of a therapeutic dose was more likely among patients randomized to receive fluoxetine. However, there were no significant differences in clinical outcomes or quality of life, nor were there any significant differences in cost, because the higher drug acquisition cost of fluoxetine was offset by lower outpatient and inpatient service use. A similar pattern of results was found at the two-year follow-up. The authors concluded that restricting the first-line use of fluoxetine in primary care would probably not reduce overall treatment costs due to the lower hospital service utilization in that group.

Other RCTs have compared SSRIs with other antidepressants and psychological therapies. One compared the costs and outcomes of fluoxetine, citalopram and amitriptyline for major depression in Europe and Central Asia and found no significant differences in cost or outcome between interventions (Hosak et al., 2000). The authors concluded that amitriptyline was no less expensive or more effective than citalopram or fluoxetine and advised that there was no advantage to restricting patients from treatment with SSRIs. Another compared SSRIs, placebo and psychological treatment for common mental disorders including depression in Goa, India (Patel et al., 2003). Psychiatric outcomes were significantly better with antidepressant than placebo at two months but no significant difference was detected at 12 months. Costs were lower in the SSRI group, suggesting that antidepressants are more cost-

effective than placebo. Psychological treatment resulted in worse outcomes and higher total costs than placebo. The authors argued that affordable antidepressants such as fluoxetine should be the treatment of choice for common mental disorders in general health care settings in India, since they are associated with improved clinical and economic outcomes, particularly in the long-term.

Retrospective analysis of existing data was used to measure the cost-effectiveness of sertraline and TCAs for depression in primary care in the UK (Forder et al., 1996). The average cost of treatment was slightly greater for those receiving TCAs due to greater use of psychiatric services. In terms of cost-effectiveness, sertraline was found to dominate TCAs for all definitions of costs and outcomes.

In an attempt to clarify the relative cost-effectiveness of antidepressants as a first choice treatment for depression in primary care, Peveler and colleagues (Peveler et al., 2005) carried out a randomized controlled trial comparing TCAs, SSRIs and the TCA-related antidepressant lofepramine. The UK-based study found no significant difference in costs or outcomes between groups. However, for values placed on an additional QALY of over £5000 – the approach taken in examining net benefits or plotting a cost-effectiveness acceptability curve – treatment with SSRIs was likely to be the most cost-effective strategy. The evidence from RCTs and retrospective analyses suggests that SSRIs are more cost-effective treatments for depression than TCAs or placebo. Despite higher acquisition costs, SSRIs do not appear to increase overall treatment costs as a result of reductions in subsequent health service utilization. In addition, SSRIs may generate better outcomes. In comparison to the limited availability of economic evaluations from naturalistic settings and RCTs, there is a plethora of studies using modeling techniques to estimate the cost-effectiveness of SSRIs for depression. These models tend to use data from existing evidence for clinical effectiveness and outcomes but expert opinion on costs and transition through the model, and are based in a variety of health systems and settings. The studies vary substantially

in the quality of the data used, the robustness of assumptions employed, the techniques used to test them and generate findings, and consequently their usefulness for this review. A decision-analytic model was used to analyze the cost-effectiveness and cost-utility of SSRIs and TCAs in various combinations for major depression in Canada and is a good example of how the evidence on the relative cost-effectiveness of the two types of antidepressant can be summarized (Canadian Coordinating Office for Health Technology Assessment, 1997). The meta-analysis of available clinical evidence showed that there were no statistically significant differences between the efficacy, completion rates and dropout rates of the antidepressants considered. The perspective of the economic evaluation was that of the health care system so only direct health care costs were included. The study suggested that from a Canadian perspective both TCAs and SSRIs should be part of an effective treatment strategy and that further research, preferably from RCTs, was needed to investigate the long-term cost-effectiveness of treatment for major depression.

In an early model Jönsson and Bebbington (Jönsson et al., 1994) compared the cost-effectiveness of paroxetine and imipramine in people with depression in the UK. The 12-month cost per successfully treated patient was lower with paroxetine than imipramine, indicating that paroxetine was the more cost-effective. The results were sensitive to assumptions concerning the relative efficacy of the drugs, particularly treatment failure, and the authors concluded that although paroxetine had a high cost per day when patient adherence and the total cost of treatment are taken into account, it was the more cost-effective option. However, these findings were questioned a few years later when the model was reassessed with some key assumptions challenged and changed (Woods et al., 1997). With revised assumptions the model demonstrated that the TCA was at least equally if not more cost-effective than the SSRI. The authors advised that a policy of using TCAs as a first choice antidepressant, with SSRIs reserved for those patients not doing well, appears more cost-effective than the reverse sequence. The two studies use the same data but generate different

results, confusing the issue of cost-effectiveness and highlighting the importance of the assumptions made in economic models.

Other modeling studies present evidence of the cost-effectiveness of SSRIs compared with TCAs (Le Pen et al., 1994; Nuijten et al., 1995) and compared to usual care (Nuijten et al., 1998) although no statistically significant differences in costs are reported. However there is evidence suggesting that SSRIs are more costly and more effective than usual care (Kind et al., 1995). When maintenance treatment with SSRIs is compared to episodic treatment with a TCA, there are improved outcomes, but alongside higher costs (Hatzianandreu et al., 1994). Evidence of the cost-effectiveness of escitalopram compared with SSRIs and other newer antidepressants is accumulating. However, the majority of the evidence is from one economic model however, applied to different health systems. In Austria, Belgium, Sweden, Norway and Finland, escitalopram was the dominant treatment strategy, achieving better outcomes with lower costs, both when health care and broader societal costs are considered for patients with severe depression (Demyttenaere et al., 2005; Francois et al., 2002; Francois et al., 2003; Hemels et al., 2004a; Lothgren et al., 2004). It was also cost-effective in treating severe depression in Austria (Hemels et al., 2004b). When the model was applied in the UK, escitalopram was found to be a cost-effective option compared with generic citalopram (Wade et al., 2005a; Wade et al., 2005b) and had a comparable cost-effectiveness profile to the newer antidepressant venlafaxine. Only one prospective evaluation of escitalopram has been carried out as part of an RCT. Fernandez et al. (Fernandez et al., 2005) demonstrated that escitalopram had similar efficacy to venlafaxine and patient costs were lower in the escitalopram group, though not significantly so. In both the models and the RCT, the reduction in costs was due to reduced hospitalization in the escitalopram group.

4.4.2 Selective serotonin and noradrenaline reuptake inhibitors (SNRI)

In common with evidence of the cost-effectiveness of SSRIs, decision and Markov models dominate economic evaluations for the newer antidepressants. The cost-effectiveness of venlafaxine for major depressive disorder has been estimated using models in a number of health care systems: Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, United States and Venezuela (Casciano et al., 2001; Doyle et al., 2001). Using results from meta-analyses, venlafaxine had the highest expected success rate and the greatest number of symptom-free days in all countries. It yielded a lower expected cost in all countries except Poland in the inpatient setting, and Italy and Poland in the outpatient setting. The authors concluded that venlafaxine is a more cost-effective treatment than the alternatives and suggested that increased utilization of the compound in most settings across Europe and the Americas would have favorable impacts on health care payer budgets. The model was reanalyzed when new data became available on the probability of relapse with different antidepressants (Casciano, 2003). The revised study disputed the treatment dominance of venlafaxine and concluded that venlafaxine was more effective than SSRIs but also more expensive.

The cost-effectiveness of venlafaxine for people in the acute phase of major depressive disorder was evaluated in a UK outpatient setting (Freeman et al., 2000). The model demonstrated that venlafaxine offered statistically significant improvements in depression-free days and, from a health care perspective, the cost per depression-free day was lower for venlafaxine than for SSRIs or TCAs. Lenox-Smith and colleagues (Lenox-Smith et al., 2004) updated the Freeman model using revised data on costs and outcomes. They found that using venlafaxine as a first-line treatment strategy, and switching to an SSRI if necessary, was a dominant treatment strategy over first-line treatment with an SSRI, resulting in better outcomes with lower costs. A similar evaluation was undertaken in Italy (Casciano et al., 1999). The results suggested that venlafaxine was more cost-effective compared to SSRIs and

TCAs for both inpatients and outpatients with respect to cost per successfully treated patient and cost per symptom-free day. Extended-release venlafaxine was found to be a cost-effective strategy among people with depression in Austria (Howard et al., 2004). Finally, venlafaxine for people with major depressive disorder has been evaluated in both inpatient and outpatient settings in Canada and the US (Einarson et al., 1995; Einarson et al., 1997; Trivedi et al., 2004; van Baardewijk et al., 2005). Results from these studies suggested that venlafaxine was more effective, but costs were either more, less or the same than with treatment with other antidepressants. The results of all the models above are highly sensitive to the assumptions made and the unit costs used. At present, and on the basis of available evidence, it is difficult to draw firm conclusions on the cost-effectiveness of venlafaxine for depression.

4.4.3 Noradrenergic and specific serotonergic antidepressant (NaSSA)

Only one study prospectively collected and analyzed data on cost-effectiveness, focusing on mirtazapine versus paroxetine in UK primary care attenders with depression (Romeo et al., 2004). Mirtazapine treatment resulted in significantly greater improvements in quality of life than paroxetine at 26 weeks. Although no significant cost differences were observed between the two groups, societal costs were lower with mirtazapine than with paroxetine. The results suggest that mirtazapine may be a cost-effective treatment choice for depression in a primary care setting.

Mirtazapine for people with moderate to severe depression has been investigated in modeling studies for the UK and Austria. In the UK study Borghi and Guest (Borghi et al., 2000) demonstrated that mirtazapine was both more effective and less costly when compared to amitriptyline and fluoxetine. The higher acquisition costs of the preparation were offset by the lower costs of managing adverse events and lower health service utilization. In Austria,

Brown and colleagues (Brown et al., 1999) established the cost-effectiveness of mirtazapine when compared to other antidepressants.

4.4.4 Serotonin modulating antidepressants (SMA)

Two models have evaluated the cost-utility of nefazodone in depression, from the perspective of a US managed care organisation (Revicki et al., 1997) and a Canadian health insurance organisation (Anton et al., 1995). In both models, cost-effectiveness was estimated for a 30 year-old woman with active depression and in both studies the findings suggested that nefazodone is a cost-effective treatment compared with imipramine (a TCA) or fluoxetine (an SSRI). The results were highly sensitive to the assumptions made in the model, particularly those concerning efficacy and dropout.

4.5 Evidence on the cost-effectiveness of antidepressants and care management

The way in which individuals starting antidepressant treatment are managed clinically may influence their outcomes and thus the cost-effectiveness of the antidepressants. Three studies have investigated the cost-effectiveness of care management versus usual care in patients starting antidepressant treatment. Care management involves patient education, shared decision-making and monitoring. In two trials clinical outcomes suggest there are no significant difference in depression-free days or in health care costs (Simon et al., 2000b; Simon et al., 2002). However, a decision-analytic model suggested that an increase in the appropriateness of care as seen in a care management programme is likely to improve functioning outcomes and increase the value of health care spending in terms of health benefits (Sturm et al., 1995).

Box 1

Summary of economic evidence on antidepressant treatments for.

What we know:

- Evidence of the cost-effectiveness of SSRIs compared to TCAs is persuasive.
- Evidence of the cost-effectiveness of the third-generation SSRI escitalopram compared to other SSRIs is accumulating.
- On the basis of available evidence, venlafaxine and mirtazapine appear to be cost-effective alternatives to SSRIs.
- New care arrangements have demonstrated their value in enhancing the effectiveness of antidepressants

What we do not know:

- Large-scale real-life (RCT or observational) comparisons of newer antidepressants to SSRIs have yet to be undertaken.
- Modeled analyses have limited application because of quality of the data on which they are based and the assumptions made.
- Most studies are based in developed countries and, given the fundamental differences in health systems across the world, it is difficult to know whether their findings can be generalized to other countries.

4.6 Economic evidence for pharmacological treatment options

The economic evidence has some limitations. Firstly, results from clinical trials are frequently inconclusive due to short follow-up periods and inadequate power to demonstrate differences in costs. Secondly, the results from economic models are strongly influenced by the assumptions made; in many cases conclusions have changed when new evidence has become available, or when medication prices have changed, or when a different view has been taken on the likelihood of an assumption (particularly in modeling studies). Notwithstanding these points, it is possible to identify some trends in the results, as well as some areas where further research is needed.

Evidence of the cost-effectiveness of SSRIs compared to TCAs is persuasive. Many studies have demonstrated that SSRIs have higher acquisition costs but lower subsequent health service costs, a pattern that may increase as SSRIs become available generically at much lower prices. Evidence of the cost-effectiveness of the SSRI escitalopram is accumulating. Although it has a higher cost than the now generic citalopram, models have demonstrated that

it achieves better outcomes and decreases the likelihood of an inpatient stay, resulting in lower costs.

Newer antidepressants have entered a crowded market, and except in one instance real-life (RCT or observational) comparisons to existing antidepressants have yet to be undertaken (or at least published). In common with other evidence from economic models, it is difficult to summarize the cost-effectiveness of these interventions. In many cases, the models that have been constructed have relied entirely on expert views to project the costs, and the precise methods used by the expert panels to arrive at their resource use estimates are often not described fully or clearly in the literature. These inadequacies limit the generalizability and applicability of these studies and make it difficult to draw firm conclusions. On the basis of available evidence, however, venlafaxine and mirtazapine appear to be cost-effective alternatives to SSRIs.

Psychotherapy is cost-effective in some patient groups, but when compared directly to antidepressants, their cost-effectiveness is unclear. The economic value of combining psychotherapy with pharmacotherapy needs further examination.

Finally, new care arrangements have demonstrated their value in enhancing the effectiveness of antidepressants, but studies have only taken place in the USA and – given the fundamental differences in health systems across the world – it is difficult to know whether their findings can be generalized to other countries.

4.7 Implications – economic evidence for pharmacological treatment options

Growing awareness of the need to improve not only the effectiveness but also the cost-effectiveness of health care interventions has produced various streams of demand for economic evidence. Two are relevant here. There are requests for measures of the overall resource or cost impact of a particular health problem, leading to cost-of-illness and ‘global

burden' studies. A lot of attention has recently focused on some of the non-health care costs – which, as we have seen, can be very large for many people with depression. While cost-of-illness calculations can be helpful in order to raise awareness of the scale and breadth of impact of mental health problems, they are no substitute for evaluations that look at both costs and outcomes. There are also demands for economic evaluations of particular treatments or policies, generating cost-effectiveness and similar analyses, either carried out within clinical trials or using routinely collected, naturalistic data. Well-conducted economic evaluations can contribute pertinent evidence to the discussion and development of policy and practice. They can support decisions relating to the funding and provision of services and can help to improve the efficiency with which scarce health care and related resources are allocated. In this chapter we have reviewed the economic evaluation evidence on antidepressant medications, drawing on a new systematic search of the international literature. The quality of many studies is disappointing. Among the methodological weaknesses are:

- small sample sizes, leaving studies under-powered to test the economic hypothesis;
- narrow measurement of costs;
- the relative rarity of randomized controlled trials, and hence few studies with strong internal validity;
- also few large observational studies with appropriate standardization, and hence limitations on the external validity of some evidence; and
- the scarcity of cost-utility analyses and cost-benefit analyses, making it impossible to use the existing evidence base to make comparisons of resource efficiency outside the mental health system.

In many areas the economic evidence relied entirely economic modelling. These models are based in many cases on expert views to project the costs, and the precise methods used by the expert panels to arrive at their resource use estimates are not described fully and clearly in the

literature. These inadequacies limit the generalisability and applicability of these studies and make it difficult to draw firm conclusions.

Economic evaluations of antidepressant treatment for depression are inherently context-bound. These evaluations describe the consequences of both the illness and its treatment for service systems and social relations, and these latter will vary from country to country, and often from locality to locality. Making generalizations across countries is therefore more difficult than with, say, clinical evaluations. The almost complete absence of economic evidence on depression treatments for all but a very few health systems of the world is therefore a further limitation.

4.8 Economic evidence for psychological treatment options

Depression is widely treated with psychological therapies including cognitive behavioral therapy (CBT), counseling and psychotherapy. Psychological therapies such as cognitive behavioural therapies and psychotherapy have proven effectiveness in depression (see section 15.1), so economic evaluations essentially aim to investigate whether high initial treatment costs are offset by potentially lower drug costs and fewer visits to other health care professionals (the cost-offset question) or if the additional costs are worth paying because of improved outcomes (the cost-effectiveness question). In standard care, psychological treatments generally tend to be delivered alongside treatment as usual, which may or may not include an antidepressant, and this is reflected in the evaluative literature. In some instances, however, antidepressants have been directly compared to psychological therapies and we concentrate on this literature here.

In an early economic analysis, 120 patients initiating treatment for depression were randomized to one of four interventions: CBT by a clinical psychologist, counseling and case work by a social worker, amitriptyline prescribed by a psychiatrist and usual care from a general practitioner (Scott et al., 1992). After 16 weeks, there were improvements in

depressive symptoms in all treatment groups, but total treatment costs were twice as much in the specialist treatment groups compared to routine care. With such a short period of follow-up, it was difficult to draw conclusions and the authors recommended a full economic evaluation with longer follow-up and one that included a wider definition of cost. More recently, Miller and colleagues (Miller et al., 2003) compared counseling and antidepressant therapy for the treatment of mild to moderate depression in primary care. At twelve-month follow-up, there were no significant differences in outcomes and costs. Bootstrap analysis showed that the antidepressant intervention was the dominant cost-effective strategy for the majority of patients, indicating that the cost-effectiveness of counseling compared to treatment with an antidepressant for depression in primary care has not been proven.

The cost-effectiveness of psychotherapy and medication was investigated in trials in Canada, the US and the UK. In one study, patients with dysthymia were randomized to interpersonal psychotherapy (IPT), IPT with sertraline (an SSRI) or sertraline alone in an RCT in primary care (Browne et al., 2002). Clinical outcomes at two-year follow-up demonstrated that there were no statistically significant differences between sertraline alone and sertraline plus IPT, but both were significantly more effective than IPT alone in reducing depressive symptoms. Societal costs were significantly lower in the IPT group, but there was no synthesis of costs and effects so the incremental cost-effectiveness of the treatment is not known. The authors stressed the importance and potential economic value of combining psychotherapy and pharmacotherapy.

IPT, pharmacotherapy with nortriptyline (a TCA) or usual care were compared in a cost-effectiveness analysis in the US (Lave et al., 1998). Both IPT and the pharmacotherapy generated better outcomes than usual care at follow-up although the pharmacotherapy group did slightly better than those assigned to IPT. Costs were higher in the IPT and pharmacotherapy groups compared to usual care. The incremental cost per QALY gained was

US\$11,695 for nortriptyline and US\$15,358 for IPT. Although the differences were not statistically significant, from a decision making perspective there is a preference for the drug treatment.

A modeled cost-utility analysis compared IPT, imipramine (a TCA), a combination of the two, and placebo in patients with recurrent depression (Kamlet et al., 1995). Modeling and simulation methods were used to estimate the costs and benefits associated with each maintenance therapy and the authors demonstrated that the drug maintenance treatment was cost-effective.

Among patients with depression who had a partner with a criticizing attitude, significant improvements in outcomes were found in patients randomized to couple therapy compared to those randomized to antidepressants (Leff et al., 2000). There were higher treatment costs in the therapy group, but the higher costs were moderated by decreased use of other services resulting in no significant differences in cost at follow-up. The authors warned that the results could not be generalized beyond individuals with depression who are living with a heterosexual partner and that conclusions were limited by large amounts of missing data in the economic evaluation.

Box 2

Summary of economic evidence on psychological treatments and antidepressants for depression.

What we know:

- **Psychotherapy is cost-effective in some patient groups, but their cost-effectiveness compared to antidepressants is unclear.**

What we do not know:

- **The economic value of combining psychotherapy with pharmacotherapy needs further examination.**

5 Diagnosis and Epidemiology 5.1

Diagnosis of depressive disorders

According to the world health organization (WHO) depressive disorders are of outstanding socio-economic and health-economic importance because they are the psychiatric disorders most frequently causing psychosocial disability as described in chapter 5.2. Despite intensive biologically oriented psychiatric research over the last decades the etiology of depressive disorders is not yet fully understood, although a multifactorial genesis is supposed. Besides psychological and social factors biological variables apparently play a major role, which lead in their whole to a disturbed central nervous homeostasis. The so-called catecholamine- and serotonin-deficiency hypothesis (Burke et al., 1995), which postulates a deficiency of monoamines (noradrenalin and serotonin) within the synaptic cleft, plays a major role in the understanding of the pathophysiology of depression. Depressive syndromes responsible to specific antidepressant therapies are classified within diagnostic entities using operationalized diagnostic systems such as the Diagnostic and statistical manual of mental disorders (actually revised version IV) (American Psychiatric Association, 1994) or the International Classification of Diseases (actually version 10) (World Health Organization, 1992). Depressive disorders are characterized by single or recurrent depressive episodes which last at least a time period of two weeks. A variety of symptoms such as affective symptoms, psychomotor disturbances, disturbances of cognition and memory, somatic complaints and psycho-vegetative disturbances are present (Table 2).

Table 2

Symptomatology of depressive disorders (American Psychiatric Association, 1994; World Health Organization, 1992; World Health Organization, 2005a)

Category of depressive symptoms	Symptom list
Affective symptoms	<ul style="list-style-type: none"> • • Depressed mood Anxiety
Psychomotor disturbances	<ul style="list-style-type: none"> • • Retardation • Agitation Loss of energy and activity
Disturbances of cognition and memory	<ul style="list-style-type: none"> • • Feelings of guilt Feelings of worthlessness • Mood congruent and -incongruent • • delusions Concentration deficits Memory deficits
Psychovegetative disturbances and somatic complaints	<ul style="list-style-type: none"> • Sleep disturbances (insomnia, early • • morning awakening) • • Diurnal changes • • Loss of appetite and weight • Sexual dysfunction Constipation Pain syndromes Hypertonia Tachycardia

To diagnose a major depressive disorder (MDD), according to the DSM-IV five main criteria of depression, according to ICD-10 a minimum of two main symptoms and 2 accessory symptoms have to be present (see Table 3 adopted from (Bauer et al., 2002b)).

Table 3

Classification and criteria of major depressive disorder (DSM-IV) (American Psychiatric Association, 1994) and depressive episode (ICD-10) (World Health Organization, 1992)

DSM-IV**Major depressive disorder****A. single episode (296.2x)****B. recurrent (296.3x)**

Criteria major depressive episode (abridged):

A Over the last 2 weeks, 5 of the following features should be present most of the day, or nearly every day (must include 1 or 2):

1. depressed mood
2. loss of interest or pleasure in almost all activities
3. significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day
4. insomnia or hypersomnia
5. psychomotor agitation or retardation (observable by others)
6. fatigue or loss of energy
7. feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach about being sick)
8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)
9. recurrent thoughts of death (not just fear of dying), or recurrent suicidal ideation, or a suicide attempt, or a specific plan for committing suicide.

B The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C The symptoms are not due to a physical/organic factor or illness

D The symptoms are not better explained by bereavement (although this can be complicated by major depression).

Table adopted from (Bauer et al., 2002b)

ICD-10**A. Depressive episode (F32)****B. Recurrent depressive disorder (F33)****Severity:**

- **mild** (F--.0): at least 2 main symptoms, plus at least 2 accessory symptoms; none of the symptoms intense
- **moderate** (F--.1): at least 2 main symptoms, plus at least 3 accessory symptoms; some symptoms marked
- **severe** (F--.2): all 3 main symptoms, plus at least 4 accessory symptoms; some symptoms severe with intensity

Criteria of depressive episode (abridged):

Minimum duration of episode: about 2 weeks

Main symptoms:

1. depressed mood
2. loss of interest and enjoyment
3. reduced energy, increased fatigability

Accessory symptoms:

1. reduced concentration and attention
 2. reduced self-esteem and self-confidence
 3. ideas of guilt and unworthiness
 4. agitation or retardation
 5. ideas or acts of self-harm or suicide
 6. sleep disturbances 10.
- loss of appetite.

Nevertheless the presence of specific subtypes within the same diagnostic group influences both the response to specific antidepressant therapies and the probability for antidepressant treatment failures. In addition comorbid conditions may influence not only the choice of specific therapies, but also safety features and the clinical effectiveness of the treatment.

5.2 Specific features of manifestations of depressive syndromes

5.2.1 Single or recurrent episodes of major depressive disorder (DSM-IV), depressive episode or recurrent depressive disorder (ICD-10)

Within both diagnostic instruments, DSM-IV and ICD-10, a variety of clinically distinguishable depressive syndromes are summarized within one diagnostic group. For estimation of both, the benefit of the treated patients during the first treatment days and the probability of response to the first antidepressant treatment trial, it is helpful to subdivide this diagnostic group in subgroups that can be separated predominantly clinically, but also using biological measures such as the activity of the hypothalamic-pituitary-adrenal (HPA)-axis. Moreover the implementation of subgroup characteristics in treatment plans and the decision which antidepressant therapeutic option should be used as a first line-treatment may enhance antidepressant effectiveness and shorten the time to clinically relevant response.

5.2.1.1 Severity of disease

Despite the fact that there is no common consensus about the exact separation of the different groups a single or recurrent episode can be classified as mild, moderate or severe depressive disorder. Besides the clinical judgment e.g. using the diagnostic criteria according ICD-10 or the Clinical global impression scale (CGI-S, Item I, severity of disease) (National Institute of Mental Health, 1976) severity groups can be separated using depression rating scales such as the Hamilton rating scale for depression (Hamilton, 1986) or the Montgomery-Åsberg rating scale for depression (Montgomery et al., 1979).

This subdivision is of clinical importance because there is broad consensus in literature that only mild to moderate depressive syndromes should be treated with psychotherapy without additional biological therapies such as pharmacotherapy or electroconvulsive therapy (ECT). Furthermore there is a distinct probability of response using phytotherapeutics such as St. Johns worth (Kasper, 2001; Laakmann et al., 1998) or benzodiazepines without antidepressants (even if this option is not recommended) (Laakmann et al., 1996) only in those subgroups of mild to moderate ill patients. Furthermore there is some evidence that especially severe

depressive syndromes show a better treatment response after ECT, using tricyclic antidepressants (TCA) or dually acting substances such as venlafaxine, duloxetine or mirtazapine.

5.2.1.2 Psychotic depression

Psychotic features of depression such as hallucinations or delusions, e.g. delusional hypochondria, feelings of guilt or nihilistic thoughts are predominantly mood congruent, but may also be noncongruent to the depressed mood. Depressive episodes with psychotic symptoms are in most cases characterized by particular severity of the disease including a high suicide risk. This additional risk factor has to be implemented in the treatment plan. In patients suffering from psychotic symptoms a combination of the antidepressant therapy with a neuroleptic medication is recommended due to the estimated better treatment outcome (Coryell, 1996). Moreover, ECT has taken into account as a possible first line treatment due to the high effectiveness during acute-treatment (Coryell, 1998) and the more favorable long-term outcome (Birkenhager et al., 2004) in this subgroup of patients, especially in comparison to pharmacotherapy (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In addition early consideration of lithium augmentation is recommended especially in this patient group in case of antidepressant treatment failures (Bauer et al., 2003; Price et al., 1983).

5.2.1.3 Treatment resistance / non-response to antidepressant treatment

About 50% of depressed patients are not responding sufficiently during a first course of an adequate antidepressant pharmacotherapy. Adequacy of treatment includes the use of a treatment with proven efficacy during a time interval of at least 4-6 weeks in a sufficient therapeutical dose range including reliable patient adherence to therapy (Fava, 2003a; Kupfer et al., 2003; Sackeim, 2001). Half of these patients fail to respond to a second antidepressant treatment trial. Some authors include the use of augmentation strategies in the definition of treatment resistance. As described further below several pharmacological treatment strategies including adjustment of dosage, switch to an antidepressant of another class, switch to an antidepressant of the same class, combination therapies with more than one antidepressant, pharmacological and non-pharmacological augmentation strategies are suitable without possibility to predict the most effective treatment strategy for an individual patient. Nevertheless the use of ECT in comparison to all of these strategies is clinically more effective (ECT review group, 2003).

5.2.1.4 Other clinical features with possible impact on antidepressant therapies

5.2.1.4.1 Catatonic features, agitated and retarded depression

Catatonic symptoms like stupor or catalepsy including severe psychomotor retardation, immobility and, on the contrary, severe agitation can be seen also in depressed patients (Fink, 1992; Starkstein et al., 1996; Taylor et al., 2003). Besides the extraordinary response to ECT (Fink, 1990; Rohland et al., 1993) which can lead to recommendations as a first-line treatment, also administration of benzodiazepines during the acute phase treatment can lead to immediate relief of symptoms. In addition in some patients suffering from agitation or psychomotor retardation a first-line pharmacologic treatment according to the influence of antidepressants on activity may be of clinical use (Kielholz, 1967; Kielholz, 1979). In clinical routine sedating antidepressants or combinations of non-sedating antidepressants with sedating benzodiazepines are used in agitated patients whereas activating substances are used in patients with predominant psychomotor inhibition.

5.2.1.4.2 Melancholic features

According DSM-IV melancholic features are characterized by a loss of the ability to feel pleasure and a variety of somatic symptoms (Table 2) and psychomotor alterations. Therapeutic consequences of melancholic features are similar to that for severe depression. Patients frequently are responding to augmentative strategies, such as combination with lithium and sleep deprivation.

5.2.1.4.3 Atypical features

According DSM-IV in *atypical depression* two of the following criteria should be present: increase in appetite and weight gain, hypersomnia, leaden paralysis and long-standing pattern of interpersonal rejection sensitivity. Empirical data support the hypothesis that (irreversible) monoaminooxidase inhibitors (MAOI) and selective serotonin reuptake inhibitors (SSRI) represent a first-line treatment option which is superior to other pharmacological treatments (Andrews et al., 1994; Henkel et al., 2006).

5.2.1.4.4 Seasonal features

Patients suffering from depression recurring on a regular annual basis during fall or early winter and spring often show subsequent symptoms of bipolar disorder (chapter 5.2.2). In addition depressive syndromes often are characterized by atypical features (chapter 5.2.1.4.3).

If depressive symptoms reach at least moderate severity no specific differences in planning pharmacologic treatments are recommended. As a difference to depressive syndromes without seasonal pattern, bright light therapy (phototherapy) can be used as an early augmentation strategy (chapter 15.3.7). Because of the proven

efficacy (Kasper et al., 1990; Rosenthal et al., 1985), bright light therapy can even be used as a monotherapy in case of mild depression during a limited treatment trial, but the possibility of enhanced suicidal ideations during phototherapy has to be taken into account (Praschak-Rieder et al., 1997).

5.2.1.4.5 Depressive syndromes in pain conditions

MDD and predominantly chronic pain are frequent comorbid conditions. Approximately 70% of patients with major depression present with physical complaints (Simon et al., 1999b). For review see also (Fava, 2002). Both, an aggravation of pain caused by somatic diseases and/or pain as a symptom within the depressive syndrome are possible and contribute to a more difficult to treat disease. In addition other psychiatric diseases like somatoform disorders, mixed psychiatric and somatic diseases such as fibromyalgia or somatic diseases, (e.g. neuropathic pain) are regularly accompanied by depressed mood and exacerbating painful conditions. The best evidence for an effective treatment of neuropathic pain exists for first generation antidepressants with a mixed serotonergic and noradrenergic mode of action such as the TCA amitriptyline (Saarto et al., 2005). In addition during the last years also evidence for the efficacy of second and third generation antidepressants in the treatment of pain conditions with and without comorbid depression have been published. The efficacy of various pharmacodynamic classes such as SSRIs, NARI, NaSSA (Mattia et al., 2002) and SNRIs (Barkin et al., 2005; Gendreau et al., 2005) has been shown. It seems plausible that antidepressants with both serotonergic and noradrenergic properties possibly are particularly effective in the treatment of pain and painful physical symptoms. Also higher remission rates in these subgroup of MDD patients have been discussed recently (Fava, 2003b). Antidepressants now are also an essential supplement within a variety of therapeutic regimes for pain.

5.2.1.4.6 Depressive syndromes in adjustment disorders

Due to the fact that the symptoms of adjustment disorders and MDD may be identical and also major depressive episodes often occur after well defined psychosocial burden, it is not justified to offer patients suffering from adjustment disorder other therapeutic regimes than MDD patients. This is especially true during the period of acute treatment. And even if controlled efficacy trials in adjustment disorders are rare, both clinical experience and retrospective studies (Hameed et al., 2005) suggest no difference in response rates within both diagnostic entities. Differences in treatment plans may be of use utilizing psychosocial therapies in adjustment disorders earlier and more intense, and maybe in shorter relapse preventing therapies if psychosocial conditions have been stabilized.

5.2.2 Bipolar depression

Diagnostic criteria for a depressive episode due to a bipolar-I disorder are the same as described already for the case of unipolar depression (see chapter 1 and Table 3). In addition there has previously been at least one manic or mixed episode including a period of abnormally and persistently elevated, expansive or irritable mood lasting at least one week (or even shorter, if hospitalization is necessary). During this time period often grandiosity or inflated self-esteem together with decreased need for sleep, hyperactivity, psychomotor agitation, racing thoughts with flight of ideas, distractibility and a pressure to keep talking causing marked impairment in social functioning is present. In case of a mixed episode these symptoms together with depressive symptoms are present at the same time for at least one week. In case of bipolar-II disorder at least one episode of hypomania, a period of manic symptoms of lesser severity which last at least 4 days has been present in the patients' history. Bipolar depression is characterized by an identical syndrome in comparison to unipolar depression. Because during the first depressive episode these information is not yet available, up to 50% of younger patients suffering from depression during the first index episode receive the diagnosis of a bipolar disorder later (Goldberg, 2003). Despite the fact of in comparison to unipolar depression more limited scientific evidence for the efficacy and effectiveness of antidepressant therapies, the same substances leading to clinical improvement in unipolar depression can be used in bipolar depression. Because of the increase of the switch-risk from depression to hypomania or mania with the antidepressant potency (defined as efficacy in pharmacotherapy resistant cases) predominantly SSRI may be considered as a first-line treatment (Grunze et al., 2002). Especially TCA, and dually acting antidepressants such as combined serotonin and noradrenaline reuptake inhibitors (SNRI) are recommended to be combined with mood stabilizers to prevent an enhanced switch risk.

Although this review is dedicated to the use of antidepressants, it should be mentioned that there is also reasonably good evidence for monotherapy with the mood stabilizers lithium and lamotrigine as well as with the atypical antipsychotics olanzapine and quetiapine (Yatham, 2005). However, there is no evidence so far that these treatment regimens may be superior in efficacy when compared to antidepressants (Möller et al., 2006).

5.2.3 Dysthymia and major depression with dysthymia (“double MDD”)

Diagnostic criteria for dysthymia and MDD differ predominantly in severity and duration. Dysthymia is characterized by a chronic depressive syndrome of lower severity in comparison to MDD. Also an additional and superimposing major depressive episode can occur in patients already suffering from dysthymia, diagnosed then as a “double depression” or “double major depressive disorder”. The differential diagnosis of both disorders is of peculiar difficulty if a dysthymic episode is following a major depressive episode, because symptoms are then indistinguishable from MDD with only partial remission, which should be diagnosed in this case. Only after a full remission lasting at least six months, the subsequent dysthymic symptoms can be diagnosed as dysthymia. Because the same antidepressant therapies are efficacious in both diagnostic entities, the acute treatment plans can be identical for MDD, dysthymia and double MDD. In addition also a neuroleptic treatment such as amisulpride (Rocca et al., 2002; Zanardi et al., 2005) may be of use. Due to the chronic nature of dysthymic disorders an earlier implementation of psychotherapeutic approaches can be of use. In addition the treatment goals should be formulated somewhat more reserved/carefully because those patients have a lesser probability for a complete recovery (Judd et al., 1998).

5.2.4 Recurrent brief depression³

Recurrent brief depression (RBD) is characterized by at least monthly occurring depressive episodes of short duration. The combination of MDD and RBD, called “combined depression” (CD), shows a relatively high prevalence. Because of the substantially increasing risk for suicidal ideations and attempts, it is of clinical use to take into consideration specific clinical properties of RBD and CD in treatment plans. In addition most trials investigating antidepressant therapies are designed to judge the therapeutic efficacy only in MDD. Different study designs are necessary to investigate RBD and CD properly. A variety of negative results after RCTs of

³ Within DSM-IV recurrent brief depression can only be diagnosed as subthreshold MDD, within ICD-10 it is a diagnostic category of *recurrent depressive disorder*

SSRIs in the treatment of RBD have been published (e.g. (Montgomery et al., 1994)), but it was hypothesized that denial of special methodological needs and highly selected patient samples have possibly been responsible for for these results (Pezawas et al., 2001). So far efficacious treatment algorithms for RBD are not yet established (Pezawas et al., 2005).

5.2.5 Major depression with comorbid psychiatric disorders

Because comorbid psychiatric disorders are a very common phenomenon in mood disorders (Pincus et al., 1999) and influence treatment outcome significantly, an implementation of the kind and duration of comorbid conditions in treatment plans for major depression is a useful procedure.

5.2.5.1 *Axis I disorders*

In more than half of the patients suffering from MDD a second axis I disorder or mixed occurrence of comorbid axis I and II disorders can be diagnosed (Pincus et al., 1999).

5.2.5.1.1 Anxiety Disorders

A lifetime prevalence of more than 40% for comorbid anxiety disorders such as panic disorder, phobias and generalized anxiety disorder, has been found in patients suffering from MDD (Hasin et al., 2005). Especially patients with MDD and comorbid panic disorder show differences in clinical course and severity of disease in comparison to patients suffering from MDD alone (Grunhaus et al., 1994).

Because the comorbid condition can diminish the clinical effectiveness of an antidepressant pharmacotherapy (Grunhaus et al., 1986) it should be taken into consideration in treatment plans. The administration of antidepressants which have shown their efficacy within both diagnostic entities, MDD and anxiety disorders together with implementation of specific psychotherapeutic options for depression and anxiety seems to be a useful strategy.

5.2.5.1.2 Substance abuse

Alcohol, nicotine and illegal drug use disorders are a common phenomenon and comorbid condition in MDD with a lifetime comorbidity of 40%, 30% and 17% respectively (Hasin et al., 2005). Because not only pharmacokinetic and -dynamic drug interactions but also psychosocial consequences of drug abuse have relevant impact on response- and recovery rates from MDD, a combined therapeutical approach addressing not only MDD but also the comorbid condition is necessary. This is especially true for psychotherapeutic and psychosocial approaches, but is also involved in pharmacological treatment plans, e.g. in choosing

antidepressants of lower pharmacological interaction potential known for some SSRI and dually acting antidepressants.

5.2.5.2 *Axis II personality disorders*

About one third of MDD patients are suffering from an additional personality disorder. The most prominent forms are obsessive-compulsive (16%), paranoid (10%) and schizoid (7%) personality disorders, but also other forms can be seen in lower rates (Hasin et al., 2005). A commonly described phenomenon is a worse treatment outcome in biological antidepressant therapies, but depression may be a positive predictive factor in the treatment of personality disorders (Shea et al., 1992). An early implementation of psychotherapeutic approaches in treatment plans together with adapted estimations about the time courses of the combined disease may be a consequence.

5.2.6 Major depression with comorbid somatic disorders

5.2.6.1 *Medical disorders*

Depressive syndromes are a very common phenomenon in severe or chronic medical disorders. Because of the homogeneity of depressive syndromes emerging from MDD, adjustment disorders, and organic depression emerging from the medical disturbance directly or from depressiogenic effects of some medication (e.g. steroids, interferon, chemotherapeutics etc.) the decision for an antidepressant treatment plan in addition to the necessary medical treatment emerges not from etiological factors. It is dependent from the severity of depression, the comorbid somatic risks and the somatic treatment.

If an organic factor is etiologically responsible for the depressive syndromes (“*organic depression*”) and the organic disease can be treated directly, in case of mild to medium severe depression treatment of the organic disease as a first line monotherapy (e.g. substitution of thyroid hormones in case of hypothyroidism) can be taken into consideration. In case of severe depression or the presence of suicide risks an additional symptomatic antidepressant treatment is obligatory. The same is true, if the organic factor can not be treated due to other conditions (e.g. immune system suppressors in case of transplantations) or is incurable (e.g. stroke). Possible organic causes for depressive syndromes are summarized in Table 4.

Table 4

Examples of organic factors possibly etiologically responsible for depressive disorders

Category of organic diseases Organic illness

Neurological disorders

- Stroke
- Dementia

- Epilepsy
- Chorea Huntington
- Hydrocephalus
- CNS infectious diseases
- CNS neoplasias
- M. Parkinson
- Narcolepsy
- Sleep-apnea
- Trauma
- M. Wilson

Endocrine disorders

- Adrenal disorders
(M. Cushing, M.

Addison)

- Hyperaldosteronism
- Hyper- or Hypoparathyroidism
- Hyper- or Hypothyroidism

Other medical disorders

- Postpartal
hormonal changes

- Neoplasias
- Cardiopulmonal diseases
- Porphyry
- Uremia

Pharmacogenic depression

- Avitaminoses
(vitamins B12, C,

Niacin or Thiamin)

- Analgesics (Ibuprofen, Indometacin, Opiates, Phenacetin)
- Antibiotics (Streptomycin, Sulfonamides, Tetracyclines)
- Antihypertensives (β -blockers, Clonidine, Digitalis)
- Chemotherapeutics (Asparaginase, Azathioprine, Bleomycine, Trimethoprine, Vincristine)
- Immune system suppressors (Mycophenolatmofetile, Tacrolimus, Corticosteroids)
- Classical antipsychotics (Haloperidol, Benperidol).

5.2.6.1.1 Cardiovascular disorders

A variety of studies confirms the interdependency between medical disorders and the risk for developing depressive symptoms caused by a comorbid MDD or an adjustment disorder. Moreover the comorbidity of MDD

and cardiovascular disorders influences the medical outcome of a coronary artery disease or a myocardial infarction significantly (Frasure-Smith et al., 1993; Musselman et al., 1998). Depression enhances cardiovascular mortality independently from other cardiovascular risk factors (Penninx et al., 2001) and seems to be an independent additional cardiovascular risk factor (Wulsin et al., 2003). The most important influencing factor seems to be the severity of the depressive syndrome (Penninx et al., 2001) or the presence of a MDD (Schulz et al., 2000). Other forms of depression seem to be less deleterious. A further important influencing factor seems to be the activation of central stress regulation systems, predominantly HPA-axis activation present in the majority of depressed patients (Lederbogen et al., 1999).

As a consequence it is important to treat depression sufficiently. It is important to use an antidepressant pharmacotherapy which has a drug-drug interaction risk as low as possible and exerts no negative influence on cardiac conductance, rhythm or output which is true for the most modern antidepressants including SSRI, NARI and dually acting substances. In addition because depression may worsen coronary blood flow (Lederbogen et al., 2001) it seems to be plausible to make use of the diminishing effects of SSRI on platelet aggregation (Maurer-Spurej et al., 2004) to achieve further benefit for patients suffering from depression and cardiovascular disease.

5.2.6.1.2 Endocrinological disorders, diabetes mellitus

Depression has been shown to be a risk factor for type II diabetes mellitus (Eaton et al., 1996), a bidirectional positive association has been assumed (Eaton, 2002; Evans et al., 2005). Also a negative influence of depression on therapeutic adherence and the risk for vascular complications and disability has been described. Vice versa endocrinological disturbances known to be present during depressive states such as hypercortisolism may be facilitating the development of diabetes. The effectiveness of antidepressant treatments in diabetic patients has been shown, but still the potential benefit for blood glucose and Hb_{A1c} levels remains unclear (Evans et al., 2005). On the other hand it has to be taken into account that antidepressants and antipsychotics with sedating properties due to antihistaminergic effects also are able to facilitate weight gain and the development of metabolic syndromes worsening diabetes mellitus markedly.

5.2.6.1.3 Renal disorders

Severe acute and chronic renal diseases can cause depressive syndromes (Kimmel et al., 2005) in adjustment disorders. They also represent psychosocial burden initiating episodes of an MDD. In both cases an antidepressant treatment plan is needed. Besides psychotherapeutic counseling also an antidepressant pharmacotherapy can be necessary. Renal failures can complicate an antidepressant pharmacotherapy in several

ways: Due to a diminished renal clearance side effects can be enhanced and toxic effects of antidepressants can be provoked. An increased responsiveness to antidepressant drugs (Finkelstein et al., 2002) together with a greater unpredictability and interpatient variability (Dawling et al., 1982) has been reported. Therefore a dose adjustment is necessary; often half of the standard doses are recommended starting the treatment. Antidepressants with a lower potential to interact with other drugs via the Cytochrome P-450 system such as the SSRI sertraline or citalopram are suggested. Frequent evaluation of side effects and in addition blood level monitoring are useful tools to prevent overdoses. On the contrary, if renal failures decompensate in end-stage renal disease and hemodialysis, hemoperfusion or hemofiltration are necessary, also lower antidepressant plasma levels are possible and dose adjustment may be required considering blood levels, efficacy and side effects.

5.2.6.1.4 Hepatic disorders

Antidepressant drugs are metabolized in the liver, and only a small proportion of some substances, e.g. 2% of paroxetine can be secreted unchanged in the urine (Tossani et al., 2005). Antidepressants are on the 5th place of drugs causing liver injury (Andrade et al., 2005). Hepatotoxic properties of antidepressants can lead to transient increases in liver enzymes, but also to fulminant liver failure. In depression accompanied by liver diseases therefore it is necessary to start treatment using substances of lower probability to cause additional liver damage. TCA and MAOI together with nefazodone seem to have higher hepatotoxicity in comparison to newer agents such as SSRI (Lucena et al., 2003). But also using SSRI and other modern substances a dose adaptation is necessary in patients suffering from liver disease due to a lower clearance of antidepressants and metabolites and therefore prolonged elimination times (Demolis et al., 1996; Joffe et al., 1998; Suri et al., 2005) to prevent side effects and intolerable toxicity. As an exception it seems to be possible to use milnacipran in case of liver impairment without the necessity of a dose adaptation (Montgomery et al., 1996; Puozzo et al., 1998).

5.2.6.2 Neurological disorders

Depression is a relatively common psychiatric comorbidity of most neurological disorders, with prevalence rates ranging between 20 and 50% among patients with epilepsy, stroke, dementia, Parkinson's disease, and multiple sclerosis (Kanner, 2005b). In addition treatment of neurological disorders, e.g. using corticosteroids enhances the risk for depression as a treatment side effect. Therefore antidepressant pharmacotherapy is mandatory in most cases of medium to severe depression. It has taken into account that vice versa antidepressant pharmacotherapy enhances the risk for worsening of the neurological condition of the treated patients. For example in patients taking high doses of antidepressants, seizure incidence rises markedly. This is particularly important using TCA;

a high risk has been described for example during maprotiline therapy. But also SSRI have the potential to prolong seizures, for example during ECT treatment (Curran, 1995) or can cause lower sodium levels lowering the seizure threshold. Nevertheless fluoxetine and fluvoxamine seem to exhibit the lowest risk (Pisani et al., 1999).

5.2.6.2.1 Epilepsy

A bidirectional relation between the incidence of epilepsy and depression has been described (Kanner, 2005a). In addition in treatment resistant epilepsy after temporal lobectomies patients often experience post-surgical depression (Kanner, 2003) and an antidepressant pharmacotherapy may be necessary. But on the contrary also a relief of depression after resective surgical treatment of epilepsy has been reported (Spencer et al., 2003). Because also lower therapeutic doses of antidepressants may be capable to trigger seizures in patients suffering from epilepsy, cautious treatment using the lowest efficacious doses is mandatory. In addition pharmacokinetic interactions between antidepressants and antiepileptic drugs have to be expected, especially with carbamazepine.

5.2.6.2.2 Stroke and dementia

It is known that patients suffering from severe depression which needs hospitalization are at an increased risk of developing cerebrovascular disorders (Nilsson et al., 2004). Patients hospitalized after stroke very often suffer not only from neurological disturbances, but show also a depressed mood requiring treatment. A concept of an “arteriosclerotic depression” has been published (Krishnan et al., 1995). In addition symptoms of depression in Alzheimer’s disease (Derouesne et al., 2004) and other forms of dementia often can be seen, but are rarely distinguishable from organic apathy, loss of drive and affective disturbances. Nevertheless symptomatic antidepressant treatment of depressive syndromes may be necessary, but it has taken into account, that meta-analyses showed no benefit concerning cognitive function or disability after treatment of post-stroke depression (Anderson et al., 2004). Even in terms of remission of the depression or disability no consistent treatment effects were seen, but benefits in terms of response to antidepressant treatment after stroke justify pharmacologic treatment (Hackett et al., 2004). But also good efficacy in preventing post-stroke depression using the NaSSA mirtazapine has been described (Niedermaier et al., 2004; Ween, 2005). Of course no adverse effects of the treatment worsening dementia for example due to anticholinergic side effects or enhancing the cerebrovascular risk could be tolerated. Therefore SSRI, NARI, SNRI and NaSSA seem to be favorable in comparison to TCA in spite of theoretical beneficial effects of their anticholinergic properties.

5.2.6.2.3 Parkinson's disease

Even if there are some controversies concerning the risk for major depression in patients suffering from Parkinson's disease (Hantz et al., 1994), an enhanced prevalence of depression in Parkinson's disease (PD) between 20-40% (Lieberman, 2006) and up to 50% (McDonald et al., 2003) has been reported. In addition depression may precede the diagnosis of Parkinson's disease (Schuurman et al., 2002). Despite the fact that no controlled studies are published and antidepressant treatment in Parkinson's disease seems to exert unspecific effects (Weintraub et al., 2005), the treatment is beneficial for the patients and improving the overall quality of life (NN, 2002). Both SSRI and SNRI treatment seems to be in most cases well tolerated and efficacious (Lemke, 2002; Menza et al., 2004). Also the potential efficacious treatment of depression during MAO-B inhibitor treatment of PD using selegiline (Bodkin et al., 2002) can be integrated in treatment plans, even if therapeutic effects on depression may be in some cases only modest (Amsterdam, 2003). The potential benefit of anticholinergic properties of TCA in PD should be taken into consideration, but due to the fact that concomitant heart disease, prostatic enlargement or glaucoma in elderly patients suffering from PD are frequent comorbid conditions the use of these substances in this patient group should be viewed with caution (Cummings et al., 1999). A moderate association of SSRI-use and extrapyramidal motor side effects in susceptible patients has been reported (Schillevoort et al., 2002). These include acute dystonia, akathisia, and aggravation of parkinsonism (NN, 2001). As the cause for these observations an interaction between serotonergic and dopaminergic pathways has been suggested (Lambert et al., 1998).

5.2.6.2.4 Encephalitis disseminata / multiple sclerosis

Even if patients suffering from multiple sclerosis often show affective disturbances without depression, also an association between multiple sclerosis and depression has been reported (Patten et al., 1997). In these cases an antidepressant pharmacotherapy should be taken into consideration.

5.2.6.2.5 Migraine

In case of migraine associated to major depressive disorder antidepressant pharmacotherapy not only ameliorates depressive symptoms but is also able to prevent migraine attacks. Both TCA (amitriptyline) and SSRI (fluoxetine) have shown their effectiveness in this indication in usual antidepressant doses (Campo-Arias, 2004). In case of migraine treatment using triptans a potentially enhanced risk for development of a serotonin syndrome in case of concomitant use of SSRI, MAOI or lithium has to be taken into consideration. Due to the relatively low rate of reported serotonin syndromes of only mild to moderate severity, the combined use of triptans and

SSRI or lithium seems to be a relative contraindication, whereas MAOI should be avoided strictly due to the limited experience published up to now (Gardner et al., 1998).

5.3 Epidemiology of depressive disorders

Depressive disorders are very common and cause worldwide the most years lost due to disability (YLD) (World Health Organization, 2002). Their lifetime prevalence is estimated to be about 16%, the 12-month prevalence has recently been reported to be about 7% (Ebmeier et al., 2006; Kessler et al., 2003). The International Consortium of Psychiatric Epidemiology (ICPE) interviewed 37.000 adults in 10 countries (in the Americas, Europe, Asia) with the WMH- CIDI (World Health Organisation Composite International Diagnostic Interview (Robins et al., 1988; Wittchen, 1994). The life time prevalence of depression varied widely from 3 % in Japan to 16.9% in the US, with most countries in the range between 8-12% (Andrade et al., 2003). In an extended WHO household survey with the WMH-CIDI of more than 60.000 adults in 14 countries (in the Americas, Europe, Middle East, Africa and Asia), the 12-month prevalence of mood disorders ranged from 0.8% (Nigeria) to 9.6% (USA) (Demyttenaere et al., 2004). These results as well as the study of the ICPE underline the potentially huge impact of psychosocial and cultural factors for the manifestation and diagnosis of depression. The European Study of the Epidemiology of Mental Disorders (ESEMeD) using similar methods as the WHO study, found a 12- month mood disorder prevalence rate of 4.2 % across 6 European nations, comparable to the results of the WHO study (Alonso et al., 2004). The low rates in Nigeria, however, might be explained by the fact that most diagnostic depression criteria and scales used in developed countries may be not appropriate to assess functional impairment in rural African communities, and that many features of depression as fatigue could be misinterpreted as signs of HIV infection. Correcting for these confounders by using appropriate scales and symptom criteria, Bolton et al found a point prevalence of even 21% for depression in Uganda (Bolton et al., 2004). For the Nigerian sample, it is also of note, as shown in a more detailed analysis of the data of that particular survey, that the most likely reason for the relatively low rate seems to be that major depressive disorder has a much later age of onset in this population (Gureje et al., 2006). The survey sample had a mean age of onset of about 30 years, but the median age of onset of major depressive disorder in the sample was about 45 years. Meaning: most of the respondents had lived through the mean age of onset. Another survey in the elderly in Nigeria confirms a much later age of onset (compared with what is commonly reported in the literature) and yields a much higher prevalence of depression.

The average age of onset is reported to be between 20 and 30 years (Ebmeier et al., 2006). Marked gender differences have been reported, women are affected twice as often as men (Kessler, 2003). The mean duration of

depressive episodes was 16 weeks, about 90% of the patients are suffering from at least moderate, up to very severe forms of depression causing severe role impairment (Kessler et al., 2003).

Highly effective and well tolerable treatment therefore is needed for all patients, but unfortunately depending on severity of the disease and gender only up to 50% of the patients are receiving any specific treatment which could be classified as adequate in up to 25% (Hamalainen et al., 2004; Kessler et al., 2003).

Improving knowledge concerning both, diagnosing and treating depressive disorders, therefore is needed within physicians and other care takers working in health services.

6 Methodology

6.1 Consensus process

Here we describe the rationale why and how this technical review has been designed so far and is planned to develop in the future. In 2005, the CINP commissioned Prof. N. Sartorius to initiate a task force to produce a full technical review on the use and usefulness of antidepressants in unipolar depression. This review is also planned to serve as documentary basis for a CINP consensus statement on this matter. The members of the Task Force are listed in this review.

A first draft was compiled by Drs. Baghai, Barrett, Grunze and Knapp and presented to the Task Force Members at a first meeting in January 2006. This review of the available evidence is based on a Medline search using appropriate search terms, books, articles and abstracts from key conferences known to the authors or brought to their attention by the other members of the Task Force and materials supplied upon invitation by the producers of the various antidepressants. After discussing the first draft, changes were made as agreed upon within the Task Force and additional topics integrated prepared by members of the Task Force and reviewed by external experts. The revised draft was then sent out for a secondary review to all members of the Task Force and, after integrating their comments, to external experts and pharmaceutical companies that have supported the project asking for their views. Comments and suggestions were again reviewed and incorporated into the third version of the draft, which was then be translated into several languages (Chinese, French, Russian, and Spanish) and discussed in several, worldwide regional meetings in the period from June to October 2006. Integrating the input of the first of these regional meetings, a pre-final draft was then be prepared and submitted to the president of the CINP in July 2006. Suggestion and comments of the governing bodies of the CINP were finally incorporated and the review finalized for publication.

6.2 Data Source

The data considered for the development of this technical review had been extracted from different sources: Medline data base until February 2006, the Cochrane library, several national and international treatment guidelines including the American Psychiatric Association (APA) Practice Guideline for the treatment of patients with major depressive disorder (American Psychiatric Association, 2000), Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments (CANMAT). Clinical guidelines for the treatment of depressive disorders (Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments (CANMAT)., 2001), Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN), Praxisleitlinien in Psychiatrie und Psychotherapie, Behandlungsleitlinie affektive Erkrankung (van Calcker D. et al., 2000) World Federation of Societies of Biological Psychiatry (WFSBP), Guidelines for Biological Treatment of unipolar depressive disorders, Part I and II (Bauer et al., 2002b; Bauer et al., 2002a), review articles from Medline-indexed journals, textbook chapters known to the authors of the draft or brought to their attention by the members of the Task Force and finally material supplied by pharmaceutical companies which accepted the invitation to support the work of the Task Force. When judging the efficacy of antidepressant treatments both original data from randomized controlled studies and metaanalyses were considered. When using metaanalyses as the primary source of evidence the authors were aware of the methodological limitation of the meta-analytic approach (Anderson, 2000b).

The CINP Task Force is also well aware of the fact that most quoted evidence in this technical review originates from clinical studies conducted in Caucasian populations in Europe and North America. Thus, results may not be representative in other populations, and both biological differences, e.g. in metabolism, and cross-cultural differences in the expression of depressive episodes may contribute to huge variability. But also cross-cultural habits in using medication may differ and influence adherence to medications, and, by this, treatment

outcome. For example, Sugahara (Sugahara et al., 2005) report an adherence rate of 66.8% over 13 weeks of antidepressant treatment in a non-psychiatric outpatient clinical setting in Japan, whereas compliance is usually worse in Western European countries and North America (Brown et al., 2005; Demyttenaere, 1998).

Therefore, special attention will be paid to the comments and suggestions at the different regional conferences, and after being reviewed by the task force, incorporated in order to improve this technical review and make it applicable on a broader basis.

6.3 Limitation

This technical review is based on publicly available materials, based on a Medline data-base search and other evidence which was brought to the attention of the authors, as detailed in the chapter before.

Thus, the reader has to be aware that this review may be subject to several biases. Failed trials are usually not published or only published with low priority and after an extensive delay, as a publication is usually not in the interest of the sponsor and may interfere with marketing strategies. Some, but not all companies have now committed themselves to an open data base policy supplying information about all controlled, company-sponsored trials on their webpage. However, using this information from some companies but not from others would also unfairly bias the results and views expressed in this review. Thus, it was decided within the Task Force to base this review only on peer reviewed, published papers and information from book chapters. Unpublished materials and abstracts were only considered if they were presented at major conferences or explicitly supplied as additional information by a company. The Task Force also expresses the hope, that an open data base policy, currently conducted only by a few companies, will become a standard so that future reviews can adequately weigh evidence in favor and against specific treatment.

Another important, yet often forgotten, methodological issue is that the fact that if two studies are significantly positive in favor of the specific medication, this does not mean that both medications are equal in efficacy. Trials are often not comparable concerning the number of included patients and the related power of statistics. When including a large n a drug placebo difference in the HAM-D of 2 may still be significant, but clinically not meaningful. On the other hand, if the power calculation was too optimistic and only a small number of patients have been included, even a HAM-D of 6 may lack significance. However, it would clearly exceed the frame work of a review to detail the methodology of each trial mentioned and we would like to refer the reader to the original publications. In addition, placebo-response rates may largely differ from study to study which may be due to different allowances of rescue medication, settings, severity of illness etc. Thus, relevant findings may be obscured by high placebo responses and may also lead to the perception that placebo could be an adequate antidepressant. Again, it would be difficult within the limitations of a review to give more detailed information for every single trial concerning all these potentially confounding factors. In conclusion, it has to be clear that a review by itself is not an unbiased and conclusive piece of evidence by itself, but it can only refer readers to the original publications. Clearly, responsible treatment decisions should never rely on comprehensive reviews, but on own critical reading of the sources.

7 Standard of care

According to WHO, fewer than 25 % (in some countries even less than 10%) of depressed patients do receive at least adequate minimal care: “Barriers to effective care include the lack of resources, lack of trained providers, and the social stigma associated with mental disorders including depression.

Primary care based quality improvement programs for depression have been shown to improve the

- quality of care,
- satisfaction with care
- health outcomes,
- functioning,
- economic productivity,
- and household wealth at a reasonable cost.” (World Health Organization, 2005a)

To achieve this mission, and similar to other psychiatric disorders (Goodwin, 2003), fundamentals of patient management in unipolar depression should include

- to receive correct diagnosis as early as possible in the course of illness,
- to have whole access to mental health and complementary services and
- finally to those in need to receive enhanced care.

7.1 *Diagnosis*

Comparing recommendations and clinical practice in different countries, there seems to be no general consensus who should establish the diagnosis of depression. Whereas most European guidelines including the WFSBP guidelines (Bauer et al., 2002b) explicitly or implicitly refer to a trained psychiatrist for establishing a diagnosis of depression, several review papers by US experts acknowledge a role for primary care physicians in establishing diagnosis and

initiating initial treatment. Most patients suffering from MDD are diagnosed and treated by general practitioners and / or well trained clinical psychologists.

Nevertheless psychiatric consultation is recommended in the case that a patient has not shown marked improvement within eight weeks of initial treatment or if the primary care physician is concerned about the complexity of the case (Wittchen et al., 2002) and also a collaboration between psychiatrists and clinical psychologists may be necessary. Besides potential cost-effectiveness consideration the main argument is that the primary care physician is generally in a better position to diagnose and treat depression if he or she is responsible for the overall medical care of the patient which may include other ongoing medical diseases with the potential of drug-drug interactions. In addition, patients tend to see in the first place the primary care physician because of somatic complains as part of the depressive syndrome. The important role of primary care physicians is also expressed by a German survey (Wittchen et al., 2002) showing that 10.9% of unselected patients visiting their primary care doctor suffer from depression. However, only 55% of them were recognized by their doctors as having depression, despite the fact that 72% of the primary care physicians participating considered their competence in diagnosing depression as good.

Thus, arguments in favor of early consultation of a psychiatrist include the complexity of a differentiated diagnosis of depressive disorders including all the considerations mentioned above and – of utmost importance – expertise in assessing the risk of suicide or, in rare cases also homicide.

If health resources are limited, e.g. in developing countries where psychiatrists and also clinical psychologists are often in very short supply, patients should have at least access to personnel with sufficient knowledge and experience to diagnose depression, e.g., general practitioners or at least trained nurses.

If resources allow, it is recommended to consider the identification of the core symptoms of depression against a checklist as DSM-IV (American Psychiatric Association, 1994) or ICD-

10 (World Health Organization, 1992) to improve confidence in and the reliability of diagnosis of depression. Structured interviews as the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) may be a helpful tool, especially if in doubt. Due to the time consuming nature of the SCID in primary care settings also the shorter Mini International Neuropsychiatric Interview (MINI) can generate reliable DSM-IV and ICD-10 diagnoses. Co-morbidity especially with anxiety disorders or substance abuse may often cover the underlying depressive illness; on the other hand, after establishing the diagnosis of depression, patients should routinely be interviewed for other major psychiatric disorders as this will impact the choice of treatment. Organic conditions such as neurological illnesses, e.g. multiple sclerosis or any other lesions involving subcortical or cortical areas, and other limbic circuits should always be excluded.

After a diagnosis of major (unipolar) depression has been established the level of symptom severity, functional impairment and impact on quality of life should be determined. If possible, this should not only be done on the basis of patients report but also on the history supplied by relatives and objective data, e.g. recent periods on sick leave. Not only to characterize the depressive syndrome, but also for choosing the appropriate treatment and treatment setting the presence of psychotic symptoms and – most important – the presence of psychotic symptoms and suicidal thoughts or plans needs to be assessed at the first visit. Especially suicidality as the outstanding threat of depressive disorders determines the further treatment plan as in some instances it maybe necessary to retain the patient against his will. With more than 10% of depressed patients committing suicide (Angst et al., 2005), acute suicidality constitutes a medical emergency that calls for immediate and consequent action. In order to obtain a full clinical picture prior to treatment, patients and, if available, relatives should be interviewed about previous illness- and treatment history, and other concurrent psychiatric and somatic disorders including non-psychiatric medication. As psychosocial stress factors may both contribute to the onset of a depressive episode and interfere with

treatment success recent life events should be documented and may lead to early psychotherapeutic intervention besides medication.

Especially in patients non responsive to treatment, the correctness of diagnosis should be rechecked regularly. Treatment success could, for example, be confounded by ongoing substance abuse or underlying personality disorders. In addition, not only when initially taking the patients history, but also during treatment patients and relatives should be questioned for emerging (hypo)manic symptoms as bipolar disorder manifests in the majority of cases first with a depressive episode. The emergence of (hypo)manic symptoms usually leads to changes in treatment plans, e.g. discontinuing antidepressants and switching to mood stabilizer treatment.

7.2 Access to Mental Health Services

The following principles of access to services are adapted from the BAP guidelines for treating bipolar disorder (Goodwin, 2003) but also apply to unipolar depression:

1. Assessment should be offered by a trained psychiatrist with an understanding of both the medical and psychological treatments available for the management of depressive disorders.
2. Patient should have access to early intervention which must include the option of hospital admission.
3. Appropriate use of legal powers of detention is mandatory for the successful management of risk in some patients with acute severe depression and suicidality.
4. Consistent outpatient follow-up is necessary and many individual patients may require more complex interventions in community settings.

Whether establishment of diagnosis and treatment initiation should be done by a primary care physician, a health professional or a trained psychiatrist has been discussed above.

Concerning the access to a trained psychiatrist without barriers, including the possibility of direct hospital admission, health and insurance policies in different countries may not yet reflect this standard or a lack of resources makes it difficult. Nevertheless, considering the consequences of inadequate diagnosis and inadequate treatment (including treatment settings) with respect to prolonged illness, chronicity and finally potential suicide, measures need to be taken to ensure these standards worldwide.

7.3 Enhanced care

Throughout guidelines (e.g. APA (American Psychiatric Association, 2000), WFSBP (Bauer et al., 2002b; Bauer et al., 2002a)) there is a uniform consensus that independent of the choice of the specific medical treatment intervention general components of psychiatric management and psychotherapeutic support should be initiated and continued throughout the entire treatment (Bauer et al., 2002b). As a first step, a therapeutic alliance has to be established. This includes that the psychiatrist or physician takes full responsibility for diagnosis, physical examination, other investigations and explanation of the medical plan of management to the patient and his relatives. He/she should take his/her time to listen to the patient's complaints and communicate always clearly, understandable and honestly what he/she thinks. He/she should determine together with the patient a treatment plan and the appropriate treatment setting and, in case of outpatients, ensure regular visits. During acute phase treatment weekly or biweekly visits are recommended (Bauer et al., 2002b), during the continuation phase and after syndromal recovery a frequency of visits of one / month appears adequate (Bauer et al., 2002b). In the case of concurrent psychotherapy supplied by a psychotherapist, frequent communication between physician and therapist about the patient's status should be ensured. Other principles adapted from Goodwin et al (Goodwin, 2003) include:

- Educate yourself and then the patient and his relatives about the disorder.

- Ensure that you are always updated about latest developments in diagnosis and treatment by continuous medical education.
- Try to base the treatment decision on evidence and not on beliefs.
- Use the evidence also to address the acute treatment modalities of the illness, the risk of relapse and the benefit of psychotherapeutic engagement to the patient.
- By educating the patient and his relatives about the illness treatment adherence may be enhanced.
- In addition, patients and relative should be informed about possible side effects of medication and potential symptoms that may question the original diagnosis, e.g. emergence of (hypo)manic symptoms.
- Make the patients aware of stressors, the impact of sleep disturbance, the importance of regular patterns of activity and early signs of relapse.
- Educate the patient about the poor outcome associated with alcohol and substance abuse and, if required, give appropriate advice and offer treatment.
- Evaluate and manage functional impairment and supply the patient and his family with a realistic view about his capacity to work and function within the family. Identify potential sources of psychosocial support in the community and help the patient to contact them.

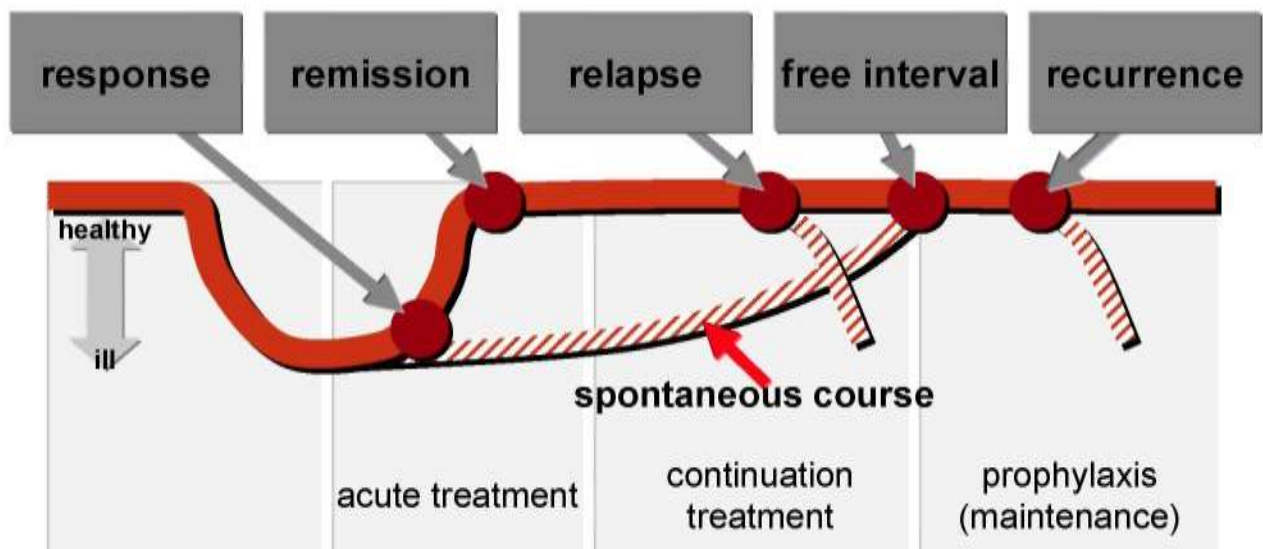
Other aspects of enhanced care, for example therapeutic drug monitoring will be addressed more specifically in the next chapter.

8 Goals of treatment - response, remission, recovery

Traditionally, treatment phases are divided into acute- continuation and maintenance (prophylactic) treatment see Figure 2.

Figure 2

Long-term treatment of depression (adopted from (Kupfer, 1991))



Clinical trials focus on symptomatic relief measured by specific scales, e.g., the Hamilton Depression Score (Hamilton Depression Rating Scale, HDRS; (Hamilton, 1967)), and define response and remission in relation to these scores (usually 50% reduction of the baseline score as “response” and a specific cut-off as “remission”). Clearly, clinical management of depression is beyond the scope of these criteria which are meant to establish evidence for efficacy of treatment.

- > Goals of clinical management can be divided into acute, intermediate and long-term goals. The ultimate goal of acute treatment is to achieve remission meaning not only being asymptomatic (in the sense of not meeting the criteria for diagnosis of the disorder and having no or only minimal residual symptoms) but also showing improvement in psychosocial and occupational functioning. The intermediate goal is

further stabilization and preventing a relapse, eliminate subsyndromal symptoms and restore the prior level of functioning. The long-term goal is to prevent further episodes, maintain functioning and ensure a satisfactory quality of life (AHCPR (Agency for Health Care Policy and Research), 1999; American Psychiatric Association, 2000; Bauer et al., 2002b).

- > From a patients perspective, most important criteria for remission are the presence of features of positive mental health such as optimism and self-confidence, a return to one's usual, normal self, and a return to the usual level of functioning (Zimmerman et al., 2006).
- > However, the utmost important goal in all phases of the illness is to prevent suicide as the most deleterious, and unfortunately still frequent outcome of depression (Angst et al., 2005).

Assessing and documenting the achievement of these treatment goals on a regular basis is of utmost importance because it guides further treatment decisions.

8.1 Acute treatment

Initiation of antidepressant treatment is always part of an overall treatment plan including optional psychotherapy, psychoeducation and psychosocial support.

Box 3

Choice of a specific drug.

With a variety of antidepressants available, proven efficacy must be the first consideration. In the next step, the choice of a specific drug should not only take into account the subtype of depression but also previous experience with antidepressants, especially potential tolerability problems in conjunction with contra-indications due to medical comorbidity, and finally the preference of the patient after explaining potential advantages/disadvantages of candidate medications.

Depending on the setting (inpatient or outpatient), the medical constitution of the patient and previous experience, the rate of titration may vary considerably. In outpatients, it is usually recommended to start with the lowest effective dose to ensure good tolerability. With no side

effects occurring or side effects fading within a few days, further stepwise dosage increases can be made until relief of symptoms is observed. If this is not the first medication trial and patients had been previously on fluoxetine or irreversible MAO inhibitors, a washout-period of at least two weeks (up to four weeks in case of switch from fluoxetine to irreversible MAOI) should be observed especially when treatment with a serotonergic acting medication is planned. Otherwise, a serotonin syndrome which is a potential lethal complication may rarely occur (Haddad, 2001). A serotonin syndrome is not just specific for SSRI, but may also occur with other serotonergic acting substances, e.g. venlafaxine in combination with MAO-I (Phillips et al., 1995). When switching to reversible MAO inhibitors, e.g. moclobemide, a few (2-3) days of pausing medication are sufficient (Dingemanse et al., 1995; Dingemanse et al., 1998). For details about MAOI tolerability see also chapter 11.6.2. On the other hand, sudden discontinuation of antidepressant treatment cannot be advised. When switching from one medication to another, overlapping tapering should be done unless a specific medication, e.g. an irreversible MAO inhibitor, demands a washout-phase (Larsen JK. MAO inhibitors: pharmacodynamic aspects and clinical implications. *Acta Psychiatr Scand Suppl* 1988; 345:74-80.:74-80.)

. Suddenly stopping treatment can lead to discontinuation symptoms which have been described for all types of antidepressant drugs, but particularly frequent with MAO inhibitors, venlafaxine and SSRIs (Baboolal, 2004; Haddad, 2001), but less frequent with escitalopram and not with the new antidepressant agomelatine. Symptoms may include agitation, sleep-disturbances, sweating, gastrointestinal discomfort and headache and may take up to two weeks to subside. These symptoms may put the patient even on risk for an early relapse (Fava, 2003a; Harvey et al., 2003) and may stress the therapeutic alliance (Garner et al., 1993). Stopping abruptly TCA treatment may put patients on risk for a cholinergic syndrome in those susceptible, especially older patients or patients with pre-existing neurological conditions

(Garner et al., 1993). When in doubt whether the symptomatology is related to drug discontinuation, reintroduction of the previous medication with consequent cessation of symptoms may clarify it.

Expectations on potential efficacy of a given treatment appear different comparing several expert reviews and guidelines. For acute treatment, different recommendations had been brought forward how long the first choice medication should be tested and when to change treatment depending on time and achieved improvement. It has been estimated that all available antidepressants produce treatment responses of 50 – 75% in moderately to severely depressed patients, which means that despite sufficient dosage another 25 – 50% of patients do not respond sufficiently to the initial treatment choice. The decision, whether a response is sufficient can be guided by the administration of established rating scales. As outlined by Rush and Kupfer (Bauer et al., 2002b; Kupfer et al., 1983) non-response would be defined as a < 25% decrease in baseline symptom severity, partial response at 26 – 49% decrease in baseline symptom severity and response as a > 50% decrease in baseline symptom severity. The WFSBP guidelines recommend that an acute phase medication trial should last at least six weeks and eight – ten weeks to define the full extent of symptom reduction (Bauer et al., 2002b). This contrasts with a recommendation from a round table consensus published by Hirschfeld et al. calling for a switch of the antidepressant in the case of non-response after four weeks of treatment. Patients remaining partial responders after six to eight weeks should receive a dose escalation, followed by augmentation or switching strategies (Hirschfeld et al., 2002) Quitkin FM, McGrath PJ, Stewart JW, Deliyannides D, Taylor BP, Davies CA et al. Remission rates with 3 consecutive antidepressant trials: effectiveness for depressed outpatients. *J Clin Psychiatry* 2005; 66(6):670-676.

. These recommendations are based, among others, on the findings of Nierenberg et al. (Nierenberg et al., 2000) showing that patients who had not received an at least 30% reduction of symptom severity by four weeks on fluoxetine, the likelihood of a response at eight weeks

was only about 12-27%. Similar findings have been reported by Stassen and Angst (Stassen et al., 1998) showing that in a controlled study comparing moclobemide and fluoxetine, onset of improvement occurred in more than 70% of patients within the first 3 weeks, and there was no evidence for pronounced improvement rates thereafter. However, there is also some evidence that especially older patients may take longer to show full response to antidepressant medication (up to 12 weeks) (Furukawa et al., 2000). To bridge the time period until onset of symptomatic improvement through antidepressants and for the acute relief of symptoms, e.g. agitation and sleep-disturbances, short-term addition of benzodiazepines maybe considered, as there is also some evidence that they may accelerate response (Furukawa et al., 2000). To establish true refractoriness in the case of a non-response or whether the previous treatment had been appropriate as far as dosage is concerned, therapeutic drug monitoring (TDM) may be helpful. TDM is based on the hypothesis that there is a well defined relationship between the drug plasma concentration and its clinical effects (therapeutic effects, adverse effects and toxicity). This hypothesis is generally well accepted for lithium and for the tricyclic antidepressants nortriptyline, amitriptyline, desipramine, and imipramine. However, results are inconsistent for other tricyclics, SSRIs, and several more recently introduced antidepressants except venlafaxine (Corruble E., Guelfi J.D. Antidepressants and major depression: relationship between efficacy and dosage in the therapeutic range ? *Acta Psychiatr. Scand.*, 2000, 101: 343-348.. Due to the economic aspects of TDM (measuring plasma levels for single psychoactive drug including its metabolites cost between 20 and 80 €) (Baumann et al., 2005), TDM should not be performed routinely, but only in cases with established serum concentration effectiveness/side effect relation and in conjunction with a clinical question, e.g. sufficient treatment response, side effects due to overdosing etc.. In addition, serum level concentration measurements should only be done under steady state conditions (at least 5 half-lives, in most drugs after one week after dosage increases/decreases) and at the time of minimal drug concentrations (trough level). Several factors may interfere

with antidepressant serum concentrations. This may include absorption and excretion of the drug, bioavailability and binding to plasma proteins. These factors determine the plasma half-life of the drug, e.g., a short (about two – ten hours) plasma half-life for venlafaxine, trazodone, tranylcypromine, and moclobemide or a very extensive plasma half-life, for example 3 – 15 days for fluoxetine.

Several potential interactions between antidepressants and other medication are due to common metabolism by cytochrome (CYP) enzymes. A genetically determined polymorphism of CYP2D6 is of high clinical relevance for antidepressants which are substrates of this enzyme including TCAs, some SSRI, venlafaxine and mirtazapine. About 5-8% of the Caucasian population are considered as poor metabolizer (PM) and 1-7% as ultra-rapid metabolizers (UM) (Baumann et al., 2005); the first leading to increased serum levels and the latter to failure of building up sufficient serum concentrations. In Asian populations, the PM type may be less frequent (about 1% in Thai, Chinese and Japanese populations and up to 4.8% in Indians (Kitada, 2003), but other enzymes may show variabilities which demand further investigations in populations other than Caucasians (Morrison et al., 2004). Concomitant medication metabolized by the same enzymes influences the metabolic rate of other substances. For example, some SSRIs as inhibitors of CYP 2D6, especially fluoxetine and paroxetine, but also bupropion, may cause clinically significant inhibition with a consequent increase in serum levels of other substrates, e.g. antiarrhythmics, beta-receptor antagonist such as propranolol or metoprolol, and opioids, e.g. codeine. Other antidepressants including imipramine, nefazodone, venlafaxine and reboxetine are metabolized by the CYP3A4 pathway, with some antidepressants showing also potent inhibition of this enzyme, for example fluoxetine and fluvoxamine (Baumann et al., 2005). Thus, TDM may become also an important tool when augmentation or combination treatments are considered in order to monitor for interactions (Baumann et al., 2005).

When the chosen antidepressant treatment is effective and symptomatic remission has been achieved it is usually recommended to continue the antidepressant in unchanged dose for continuation treatment unless side effects may force tapering down. It is also recommended to continue the full dose of acute treatment which induced remission during maintenance phase. Frank et al. (Frank et al., 1990) and Franchini (Franchini et al., 1998) demonstrated that patients who received during maintenance only half of the acute phase dose of imipramine or paroxetine, respectively, rather than the full dose showed a significantly higher recurrence rate. Thus, the often applied clinical practice of dose reduction for maintenance treatment lacks an evidence base and may put the patient on an increased risk of relapse. The situation may be different when full response was already achieved with low dose antidepressants during acute treatment; in this case, it may be justified to continue treatment in the lower dose range (Furukawa et al., 2003).

8.2 Continuation treatment

After initial remission from acute depression, continuation treatment should ensure stabilization, prevention of early relapses and improve further functionality and foster reintegration. It is generally recommended to continue with the effective antidepressant monotherapy or combination treatment for at least another three to six months ((Hirschfeld, 2000), see also Table 5), but patients with a history of long previous episodes may be candidates for longer continuation phase treatments (Ramana et al., 1995). In a prospective 15-month follow-up study in depressed patients persisting residual symptoms are strong predictors of subsequent early relapses, which occurred in 76% (13/17) of those with residual symptoms and 25% (10/40) of those without (Ramana et al., 1995). Therefore it is strongly recommended to continue treatment until all symptoms have totally subsided (Prien, 1990).

Table 5

Selected guidelines for duration of antidepressant treatment after acute treatment response
(from Geddes et al. (Geddes et al., 2003))

	Recommended duration of continuation* after medical management of the acute episode (months)	Number of episodes that would indicate longer "maintenance" treatment is appropriate
UK defeat depression consensus statement ⁴	4–6	≥2
US Agency for Health Care Policy and Research ⁵	4–9	≥3
British Association for Psychopharmacology ⁶	6	≥3 in past 5 years (or ≥6 in total)
American Psychiatric Association ⁷	4–5	Not specified

*At same dose.

However, for patients with a previous, untreated episode in their history, the individual duration of continuation treatment can be determined by questioning for the time elapsed until spontaneous recovery occurred. For example, if a previous untreated episode lasted nine months, continuation treatment of this episode should now last at least for the same time period.

8.3 Maintenance treatment

If a decision for long-term maintenance treatment (prophylaxis against new depressive episodes) has been made the transition from continuation to prophylaxis is not clear-cut. However, if there is no indication for prophylaxis or the patient refuses to continue on

medication, slow tapering off at the end of continuation is strongly advised. It has been suggested that the tapering phase should last at least four to six months (Bauer et al., 2002b). Maintenance treatment is most commonly appropriate for patients with recurrent episodes, especially when an episode prior to the present one has occurred during the last five years or when remission has been difficult to achieve. Other factors influencing the decision in favor of maintenance treatment include the number as well as the severity of previous episodes, the duration of previous symptom-free intervals and comorbidity with other psychiatric or medical illnesses. Some guidelines, e.g. the WFSBP Guidelines recommend maintenance treatment of five – ten years in recurrent patients not on special risk. Life-long maintenance should be considered in patients at greater risk, e.g., with more severe episodes, and especially when two or three attempts to withdraw medication have been followed by another episode within a year (Bauer et al., 2003). However, there are no controlled studies available assessing the optimal length of maintenance treatment or how to identify clear predictors for choosing an individual time span. A literature review by Fava (Fava, 2003a) raised the question whether at least a substantial subgroup of depressed patients may not only have no profit from maintenance medication but even experience a worsening of the long-term course of the illness. According to Fava, the mechanism of this paradox effect may include occurrence of tolerance to antidepressants in long-term treatment, onset of resistance upon each challenge with the same antidepressant and withdrawal symptoms with sudden discontinuation of antidepressants leading to destabilization. Fava speculates that continued drug treatment may initiate biological processes counteracting the initial acute effects of a drug and may result in loss of clinical effectiveness. With sudden drug discontinuation these processes may operate unopposed at least for some time and increase vulnerability to relapse. Whereas a multitude of clinical studies including a metaanalysis of long-term treatment (Geddes et al., 2003) clearly support the efficacy of antidepressant maintenance in clinical

trials subjects, the role of long-term antidepressant continuation in less severely depressed patients still needs further clarification.

8.4 Management of side effects

Patients complaints about side effects of the medication should always been taken seriously, otherwise non-adherence and uncontrolled discontinuation will be the consequence. However, patients do not always report spontaneously about side effects, so active exploration is recommended. In case of a full or at least partial responsiveness and the willingness of the patient to continue on the medication despite side effects, careful tapering of the medication would be the first step. If side effects occur already at unusual low doses, TDM and potential identification of a poor metabolizer status may be helpful (Baumann et al., 2005). If after tapering of medication side effects do not reside or efficacy is lost, switching of medication with slow tapering off and tapering in of a new antidepressant is advised. In general, SSRIs and mixed serotonergic/ noradrenergic antidepressants have a more favorable side effect profile than older TCAs or irreversible MAO inhibitors (Kahn et al., 2005). But also those newer antidepressants may be not as well tolerated as generally assumed. The frequency of their side effects may be underestimated because clinical trials often only report on spontaneously reported side effects, and in natural settings they may be much more common. In the context of management of side effects psycho-education of the patient has a prominent role. Experience of side effects is less frightening if the patient is aware about their possibility, and especially with side effects that may subside after some days, like increased sleepiness, informed patients may be more likely to tolerate it and to stay on medication.

9 Specific age and gender related conditions

9.1 *Gender related differences*

Gender differences in unipolar depression are a consistent finding in several longitudinal and cross-sectional studies (for review see (Kahn et al., 2005; Kuehner, 2003). The lifetime prevalence shows an unadjusted mean female/male ratio of 2.1 whereas the point prevalence gender ratio is 1.7 (Kuehner, 2003). This estimate of differences in lifetime depression rates is calculated from large population- based studies including up to almost 45000 and, for point and period prevalence rates even up to 78000 people (DEPRES study (Depression Research in European Society), (Angst et al., 2002b)).

Several differences in co-morbidities, symptomatology and coping style between genders have been described. Starting with co-morbidities, frequent disorders co-morbid with depression in females include anxiety (Breslau et al., 1995), somatoform disorders and eating disorders, especially bulimia (Marcus et al., 2005) whereas men are more likely to suffer from co-morbid alcohol and drug abuse (Marcus et al., 2005). In part, this may also be reflected in the coping style with depression. Thus for example Angst et al. found that depressed men were more likely to increase consumption of alcohol whereas women tried to cope through emotional release and religion (Angst et al., 2002b).

As far as other features of depression are concerned, recently published results of the STAR-D study (Marcus et al., 2005) also showed a significantly earlier onset of the first major depressive episode in women, and longer current major episodes for women when compared to men. In addition, some features of depression appear more prevalent in men than in women, for example a tendency to overreact and anger attacks (Winkler et al., 2005). Criterial major depressive episodes according to DSM IV (American Psychiatric Association, 1994), however, are more prevalent in female than male depressed patients (Angst et al., 2002b). In

the large European DEPRES I and II-study women were significantly more likely to have five or more criterial symptoms of depression than men (female/male ratio 1.96). Interestingly, differences in symptomatology are already apparent in adolescent depression. Bennett et al. (Bennett et al., 2005) interviewed 383 depressed adolescents with the Childhood Version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-IIIR, IV, (Bennett et al., 2005)) and the Beck Depression Inventory (BDI, (Bennett et al., 2005)). In this sample with a mean age of 15.8 years, he found that depressed girls were more likely to exhibit guilt, body image dissatisfaction, self-blame, self-disappointment, feelings of failure, concentration problems, difficulty working, sadness/depressed mood problems, fatigue and health worries than depressed boys. In contrast, depressed boys had higher clinician ratings for anhedonia, depressed morning mood and morning fatigue (Bennett et al., 2005). Explanations for these gender differences are manifold and several factors may contribute to these differences in illness characteristics. According to Kuehner (Kuehner, 2003), genetics, sex hormones, different endocrine stress reactivity, a higher incidence of thyroid axis abnormalities, prior anxiety disorders, personality traits, neuropsychological factors, gender role and psychosocial factors, and life events, e.g., childhood sexual abuse may contribute to these differences. So far, there are no consistent findings for gender differences in heritability (Kendler, 1998). Only when broadening the criteria for major depression, heritability for major depression seems to be greater in women than in men (Kendler, 1998). In elderly patients, a higher heritability for depressive symptoms may be associated with female gender (Jansson et al., 2004). In addition, gender-specific genetic polymorphism may play a role for different responsiveness and speed of onset of antidepressant action, e.g. the Angiotensin I converting enzyme (ACE). In women, D/D and I/D alleles had been associated with a faster onset of different antidepressant therapies (Baghai et al., 2003; Baghai et al., 2004). Overall, however, more research is still needed to come to firmer conclusions concerning a gender specific genetic preposition for depression and response to treatment.

Sex hormones may play an important modulatory role for the manifestation and course of depression, and also for treatment response. Thus depressive symptomatology in vulnerable women seems to increase when their physiological estradiol levels decrease, e.g. perimenstrually, in the postpartum period or during perimenopause. At the same time several studies have shown estrogen treatment to be effective in postpartum as well as perimenopausal depression (for review see (Kahn et al., 2005; Riecher-Rössler et al., 2006)). Estrogens may enhance serotonergic activity and, if combined may induce a better responsiveness to SSRI ((Stahl, 2001), for review (Kahn et al., 2005)). Estradiol may be involved in desensitization on the 5HT_{1A} receptor (Bouali et al., 2003; Carrasco et al., 2004). Other neuroendocrine axis as the HPA (Kornstein et al., 2002) and thyroid axis (Kornstein et al., 2002) may also exhibit subtle differences between genders, and, by this, cause a different vulnerability to depression.

Clinically, gender differences in treatment response had been demonstrated in several studies (Frank et al., 1988; Kornstein et al., 2002; Yonkers et al., 2002), but could not be confirmed by other studies (Scheibe et al., 2003; Thiels et al., 2005) or combined analysis of several studies (Hildebrandt et al., 2003). When interpreting data especially from randomized controlled studies, a major methodological pitfall is the under-inclusion of women in the older studies (Yonkers et al., 2002). This makes especially results on a potential gender specific efficacy of tricyclics difficult to interpret. This situation is slightly different with SSRIs where reported gender differences are based on more recent studies with equal gender distribution. In a review of 30 randomized, placebo-controlled trials of tricyclics conducted to obtain market authorization between 1979 and 1991 Wohlfarth et al. (Wohlfarth et al., 2004) could not identify a gender difference for the efficacy of tricyclics. This contrasts with a meta-analysis of Hamilton et al. (Hamilton et al., 1995) of all published trials with imipramine showing significantly different response rates of 62% for men and only 51% for women. On the other hand, several studies describe a significantly higher response rate for women to

SSRI treatment when compared to men, e.g. (Baca et al., 2004). A better efficacy of SSRIs could also be demonstrated by an analysis of 15 randomized, placebo-controlled studies conducted at the Northwest Clinical Research Center in Bellevue WA. between 1996 and 2003 (Khan et al., 2005). They found that women had a significantly greater response than men to SSRI but not to SNRI antidepressants. The authors assume that this different responsiveness may be due to subtle differences in the serotonergic system between men and women (Bano et al., 2004; Bell et al., 2001; Nishizawa et al., 1997). For other classes of medications, gender specific differences are less clear. For example, better response rates to MAO inhibitors (MAO-I) in women have been described in studies including a substantial number of depressed patients with so called “atypical features” (Davidson et al., 1986). However, “atypical depression” characterized by dysphoria and pronounced anxiety, is a more likely finding in women than men, and MAO inhibitors had previously demonstrated a good efficacy in this condition (Henkel et al., 2006). Thus, the finding of higher responsiveness to MAO-I for women may simply be due to the interaction of depression subtype and gender. This is a good example that careful consideration of potential co-variables is essential in order to identify true gender differences. In summary, neither prevalence or symptomatology nor treatment response or consequences of depression are identical in men and women, and a gender specific psychiatric approach, taking into account gender-specific risk- and influencing factors - including gender roles -, is warranted (Riecher-Rössler, 2000).

9.2 Age related differences

9.2.1 Using Antidepressant Medications to Treat Depression in Child and Adolescent Populations

9.2.1.1 Introduction

Identifying and treating major depression in child and adolescent populations is often more complicated than in adult populations for two main reasons. First, the clinical features of depressive disorders in young patients may differ substantially from those of adult patients. Instead of manifesting neurovegetative or straightforward depressive symptoms, depressed children may exhibit behavioral problems causing difficulties in psychosocial functioning at home or at school. Identifying these behaviors related to and underlying depression requires not only evaluating the patient, but also talking to parents and teachers as informants. The second difficulty stems from the variety of treatment options based on relatively little evidence of efficacy and safety in children and adolescents. In addition, questions have been recently raised recently regarding the possibility of increased suicidal behavior in depressed youth treated with antidepressant medications (Leslie et al., 2005). All of these issues must be considered before deciding whether and how to treat depressed youth. Comprehensive guidelines about identifying and treating depressed youth have been published elsewhere (Birmaher et al., 1998; Park et al., 2000). Likewise, comprehensive reviews of evidenced-based psychotherapies for youth depression are available (Compton et al., 2004; Curry, 2001). This chapter instead will discuss the safety and efficacy of antidepressants in child and adolescent populations. First, randomized controlled trials (RCTs) of antidepressants in depressed children and adolescents will be reviewed. Next, regulatory actions taken by drug safety agencies in the United States (US) and United Kingdom (UK) will be discussed. Finally, recommendations regarding pharmacologic treatment of depressed children and adolescents will be offered.

9.2.1.2 *Psychopharmacology of Major Depression in Youth*

While empirical studies of antidepressant medications have been conducted in depressed child and adolescents populations since the 1960s, the first well-designed, double-blind, placebo-controlled studies – most involving tricyclic antidepressants (TCAs) – did not take place until the mid and late 1980s (Ambrosini, 2000). Since then, several RCTs, primarily of newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been conducted in child and adolescent populations. No RCTs of monoamine oxidase inhibitors have been conducted in depressed child or adolescent populations.

A Cochrane meta-analysis of TCAs, as well as all known published and unpublished RCTs of SSRIs and atypical antidepressants, will be described below. Whenever applicable, a distinction will be drawn between a given drug's attributes in child (age 12 and under) as compared to adolescent (age 13 and older) populations.

9.2.1.2.1 Tricyclic Antidepressants

Given the ample evidence for efficacy in adult populations, multiple clinical trials of tricyclic antidepressants -- including studies of amitriptyline, imipramine, nortriptyline, and desipramine -- have been conducted. A Cochrane Review of 13 of these RCTs involving over 500 youth was completed by Hazell and colleagues (Hazell et al., 2002). Across child and adolescent populations, the effect size (ES) identified by this meta-analysis was statistically significant, but small (ES = -0.31, 95% confidence interval -0.62 to -0.01; negative effect size indicates a reduction in depressive symptoms). However, when subgroup analyses were conducted, no significant benefit was seen with children (ES = 0.15, 95% CI -0.34 to 0.64), but a larger advantage was seen with adolescents (ES = -0.47, 95% CI -0.92 to -0.02). This differential treatment response is consistent with TCAs superior efficacy in adult populations, and may be explained by maturation of neurological pathways or other developmental differences between children, adolescents and adults (Bostic et al., 2005). Importantly,

compared to placebo controls, TCA were associated with more vertigo, orthostatic hypotension and dry mouth in pediatric populations (Hazell et al., 2002).

9.2.1.2.2 SSRIs and Newer antidepressants

Given the lack of convincing evidence of effectiveness and narrow therapeutic window of TCAs, more recent pediatric depression trials have focused on SSRIs and atypical antidepressants. However, while seventeen placebo-controlled RCTs of newer antidepressants have been conducted, only eleven have been published [or are in press] (Table 6). This section describes the published and unpublished SSRI trials both with regard to efficacy and safety. Data regarding unpublished trials were obtained from the report completed by the UK's Committee on Safety of Medicine (CSM) of the Medicines and Health care products Regulatory Agency (Committee on Safety of Medicines, 2006), and two recent reviews of antidepressants in youth depression (Bostic et al., 2005; Cheung et al., 2005).

Table 6

Published, placebo-controlled, randomized clinical trials of SSRIs and newer antidepressants in children and adolescents

Agent	Author	N	Study Characteristics				Primary Outcome	Results				Sponsor
			Age	Dose (mg)	Length (weeks)	Sites (#)		Active Treatment	Placebo	P value	Sig. ? (Y/N)	
Fluoxetine	(Simeon et al., 1990)	40	13-18	20-60	8	1	none assigned	n/a	n/a	n/a	N	n/a
	(Emslie et al., 1997)	96	7-17	20	8	1	CGI-I (1 or 2) CDRS-R mean scores	56% 38.4	33% 47.1	.02 <0.008	Y Y	NIMH
	(Emslie et al., 2002)	219	8-18	20	8	15	CDRS-R (I >= 30%) CGI-I	41% FLX+ CBT: 71.0%	20% 34.8%	0.09 .001	N* Y	Lily
	(March et al., 2004)	439	12-17	10-40	12	13	(1 or 2) change in total score (adj mean) HAM-D (<= 8 or ↓>=50%)	60.6% CBT: 33.79 FLX: 36.30 66.5%	34.8%	.001	Y	NIH
	(Keller et al., 2001)	18	12-18	20-40	8	10	HAMD (change from baseline) MADRS (I >= 50%)) K-SADS-L (change from baseline)	41.77 33.79 36.30 66.5%	41.77 55.2%	.001 .34 .11	Y N N	GSK
	(Berard et al., 2006)	286	13-18	20-40	12	33	CDRS-R (change from baseline) CDRS-R (mean reduction)	18.98 ->8.24	19.79->9.88	.13	N	GSK
	(Emslie et al., 2006) (Wagner et al., 2006)	206 376	7-17 6-17	10-50 50-200	8	40	CDRS-R (change from baseline) CDRS-R (change from baseline)	n/a	n/a	.684	N	GSK
Sertraline	r et al., 2003)				10	53	(mean reduction)	-22.84	-20.19	.007	Y	Pfizer
Citalopram	(Wagner et al., 2004)	174	7-17	20-40	8	21	CDRS-R (change from baseline)	36%	24%	<0.5	Y	Forrest
Escitalopram	(Wagner et al., 2006)	264	6-17	10-20	8	25	CDRS-R (change from	-21.9	-20.2	.310	N	

baseline)

Venlafaxi ne	(Mando ki et al., 1997)	40	8- 17	37. 5- 75	6	1	n/a	n/a	n/a	n/a	N	n/a
-----------------	-------------------------------	----	----------	-----------------	---	---	-----	-----	-----	-----	---	-----

*Authors note that results would have reached significance if response was defined as decrease in CDRS of 20%, 40%, 50%, or 60%>/= ;

**Trial included 275 subjects; but 95 were randomized to imipramine and not considered in above analysis; n/a = not available; GSK = GlaxoSmithKline

9.2.1.2.2.1 Fluoxetine

Between 1990 and 2004, four trials of fluoxetine as a treatment for child and adolescent major depressive disorder have been conducted, three of which were positive. The negative study of fluoxetine which was small and possibly underpowered involved 40 adolescents from inpatient and outpatient settings. After 8 weeks on 20-60mg of fluoxetine, authors did not identify significant differences on any of the outcome measures used; subjects responded equally well to fluoxetine or placebo. Other than weight loss, no drug-associated adverse events were reported (Simeon et al., 1990).

The first positive fluoxetine study, published in 1997 by Emslie et al, compared a fixed-dose of fluoxetine 20mg to placebo in a group of 96 children and adolescents ages seven to 17 (Emslie et al., 1997). Youth were treated for eight weeks at a single site. At the trial's end, compared to the placebo condition, youth assigned to fluoxetine scored significantly better on both prospectively-identified primary outcome measures, the Clinical Global Impressions-Improvement Score (CGI-I) and the Children's Depression Rating Scale-Revised (CDRS-R). Significantly more youth in the fluoxetine condition "responded" (i.e., received ratings of 1, "very much improved" or 2, "much improved" on the CGI-I). While endpoint mean CDRS-R scores were significantly better for fluoxetine-treated youth than for those who received placebo, the differences in terms of "remission" (a dichotomous measure, prospectively defined as a score of <29 on the CDRS, and potentially less sensitive to change) did not reach significance. Response rates did not differ for children 12 and under compared to adolescents

13 and over. When compared to placebo, adverse events were not significantly increased in the fluoxetine-treated group.

In 2002, Emslie et al published an eight-week multi-site follow up study of 219 eight to 18 year olds (Emslie et al., 2002). In this trial, the CDRS-R was again used as a primary outcome measure. While the mean 22-point drop in CDRS-R scores in the fluoxetine group was significantly different from the 14.9 point decrease noted in the placebo group, it did not achieve primary outcome “response” criteria prospectively defined as a $\geq 30\%$ decrease in scores. However, in post-hoc analyses the authors demonstrated that primary outcome would have been achieved had response been defined at $\geq 20\%$, 40% , 60% or 70% decrease in CDRS scores, or if their calculation correctly reflected the fact that CDRS-R scale has a minimum value of 17 instead of 0 (Cheung et al., 2005). While no information was provided regarding suicidality, patients receiving fluoxetine reported fewer adverse events than did those receiving placebo. Based on these results, fluoxetine received FDA approval to treat child and adolescent MDD.

In the double-blind relapse-prevention phase of the above study, Emslie and colleagues continued to follow 40 subjects who remitted on fluoxetine; 20 of these fluoxetine-responders were assigned to continue fixed dose fluoxetine, whereas 20 others were changed directly from fluoxetine to placebo. Over the subsequent 32 weeks, when compared those switched to placebo, fewer subjects who remained on fluoxetine relapsed (60% vs. 34% respectively). Additionally, time to relapse was longer for those who remained on fluoxetine compared to those who were switched to placebo (181 days vs. 71 days; $p=.046$). There were no statistically significant differences in adverse events (Emslie et al., 2004). Fluoxetine, alone and in combination with cognitive-behavioral therapy (CBT), was compared to placebo in the Treatment for Adolescents with Depression Study (TADS). This first phase of this landmark NIMH- (National Institute of Mental Health) sponsored multisite RCT followed 439 adolescents (ages 12-17) with moderate to severe depression for 12 weeks. The

fluoxetine plus CBT condition was superior to placebo on both primary outcome measures: CDRS-R total score and CGI-I score of 1 or 2. Fluoxetine alone was statistically superior to placebo on the CGI-I variable, but not the CDRS-R. Compared to placebo, there was a statistically significant increased risk of harm-related events -- a category which included suicidal or non-suicidal behavior such as self-cutting -- in the groups treated with fluoxetine (odds ratio 2.19; 95% CI 1.03 – 4.62); however, there was not a statistically significant increased risk of suicide-related events in the fluoxetine condition. While suicidal thinking decreased in all treatment groups, the fluoxetine plus CBT condition was associated with the greatest reduction (March et al., 2004).

9.2.1.2.2.2 *Paroxetine*

Keller et al treated 180 adolescents (ages 12 to 18) with either paroxetine or placebo in a multi-site, eight-week RCT. The Hamilton Depression Scale 17-item version (HAM-D-17) was the primary outcome measure; both response (end of trial score of ≤ 8 or a $>50\%$ reduction) and change from baseline were assessed. While youth treated with paroxetine improved on primary outcome measures relative to placebo, these improvements were not statistically significant in case of imipramine (Keller et al., 2001). Adverse events were reported more often by patients receiving paroxetine (11 patients) versus placebo (2 patients). Additionally, paroxetine-treated patients had an increased risk of suicidal ideation compared to placebo-treated patients (5.4% vs. 0% respectively).

Two additional paroxetine studies, both conducted several years ago and previously unpublished, have recently been published (Berard et al., 2006) or are now in press (Emslie et al., 2006). Neither study demonstrated efficacy of paroxetine compared to placebo on primary outcome measures. In the first study (Berard et al., 2006), which focused on adolescents ages 13-18, more treatment-discontinuing adverse events and suicide-related behavior were reported in the paroxetine group compared to placebo (11.8% vs 7.1% and 4.4% vs 2.1% respectively; these differences were not statistically significant). In the second study, (Emslie

et al., 2006) which evaluated paroxetine in 206 children ages seven to seventeen, serious adverse events were more commonly reported by children treated with paroxetine (six youth) versus placebo (one youth). Additionally, treatment discontinuation due to an adverse event occurred more commonly in the paroxetine condition (8.9%) versus the placebo condition (2%).

9.2.1.2.2.3 *Sertraline*

In 2003, Wagner et al published the combined results of two separate ten-week trials involving 376 child and adolescent subjects (ages 6 to 17) with MDD (Wagner et al., 2003). These studies were conducted at 53 sites in five countries, and the combined analysis was planned a priori. While the individual trials did not reach statistical significance on the primary outcome measure (mean reduction in CDRS-R), when combined they demonstrated a small but statistically significant effect. Of note, at the study's endpoint, the mean difference in CDRS-R score was significant for adolescents (sertraline: -28.95; placebo -24.11; $p = 0.01$) but only borderline significant for children (sertraline: -31.44; placebo -27.56; $p = 0.5$). When compared to placebo, three times as many sertraline-treated subjects discontinued treatment as a result of suffering adverse events.

9.2.1.2.2.4 *Citalopram*

Wagner et al also published results from an eight-week trial of citalopram in 174 children and adolescents (ages 7-17) with MDD (Wagner et al., 2004). When compared to placebo, response criteria (CDRS-R ≤ 28) was achieved by significantly more citalopram-treated depressed youth. Citalopram and placebo were discontinued due to adverse events at a similar rate (5.6% and 5.9% respectively). No differences between child and adolescent populations were reported.

According to the CSM report, a large unpublished trial of citalopram in depressed teenagers (13-18) did not demonstrate antidepressant effect when compared to placebo. Additionally,

when compared to placebo, greater percentages of citalopram-treated youth reported self harm or suicidal thoughts, made serious suicide attempts, and required hospitalization.

9.2.1.2.2.5 *Escitalopram*

Wagner and colleagues conducted an eight-week RCT of escitalopram, the S-isomer of citalopram, involving 264 youth ages six to seventeen (Wagner et al., 2006). While the results of this study have not yet published, but have appeared in a review (Bostic et al., 2005). According to Bostic and colleagues, while the results across the entire sample did not reveal significant differences, subgroup analysis revealed a statistically significant drug versus placebo benefit for adolescents. Rates of discontinuation due to adverse events and rates of suicide-related behavior were similar in the drug and placebo conditions.

9.2.1.2.2.6 *Venlafaxine*

Venlafaxine, an antidepressant that inhibits reuptake of both serotonin and norepinephrine, has also been evaluated as a treatment for depressed youth. In 1997, Mandoki et al published a trial involving 40 children and adolescents (ages eight to 18), who received relatively low doses of Venlafaxine (37.5mg for children, 75mg for adolescents) or placebo; all subjects also received a weekly therapy with cognitive and behavioral elements. After six weeks, a significant improvement was noted in all subjects; however, there was no significant difference between the venlafaxine-treated subjects and those who received placebo. No serious adverse events were reported in the published paper; however, one subject was hospitalized after developing mania (Mandoki et al., 1997).

Emslie et al conducted two RCTs of Venlafaxine XR in a total of 334 seven to 17 year-olds with MDD; while unpublished, the results of these two trials were analyzed together and described in a recent review (Cheung et al., 2005). The combined analysis did not identify any significant differences between venlafaxine ER and placebo on the primary outcome variable of CDRS-R endpoint. Of note, when children (ages seven to 11) and adolescent (ages 12 – 17)

subgroup analyses were conducted, there was a suggestion of efficacy in adolescent group (Cheung et al., 2005). According to the CSM report, more treatment discontinuing adverse events, including hostility and suicidality, were identified in the group treated with venlafaxine.

9.2.1.2.2.7 Mirtazapine

Emslie et al also conducted two RCTs of mirtazapine, a noradrenergic and specific serotonergic agent. These trials involved a total of 250 depressed youth (ages 7 to 17). While the results of these trials remain unpublished, a recent review indicates that no significant CDRS-R differences between mirtazapine and placebo conditions were noted at the end of either eight week trial (Cheung et al., 2005). According to the CSM report, one mirtazapine-treated subject reported suicidal thoughts and one placebo-treated subject performed an act of self-mutilation.

9.2.1.2.2.8 Nefazodone

Two RCTs of nefazodone, a serotonin modulating antidepressant, have been conducted by Emslie and colleagues. While neither study has been published, one trial involving 195 depressed 12 to 17 year olds was described in a recent review (Cheung et al., 2005). In this study, beneficial effects for nefazodone approached but did not achieve statistical significance on CDRS-R primary outcome variable. No nefazodone-related serious adverse events occurred. The CSM report included no data regarding this medication.

9.2.1.2.2.9 Bupropion

No RCTs have been conducted with this medication in child and adolescent populations.

9.2.1.3 Regulatory Action by the UK and US

In June of 2003, after evaluating unpublished manufacturer data revealing increased suicidality associated with paroxetine, the UK Committee on Safety of Medicine (CSM) advised that paroxetine should not be used to treat depressed youth. The US Food and Drug

Administration (FDA) quickly followed suit. In August 2003, the manufacturer of venlafaxine sent letters to doctors explaining that, due to lack of efficacy and potential for increases in suicidality and hostility, this drug should not be used in youth. By December 2003, MHRA warned against using all SSRIs and the FDA urged extreme cautions when using any newer antidepressant in pediatric populations (Leslie et al., 2005).

Given their concern for treatment-emergent suicidality, the FDA conducted a review of independently-coded safety data from 24 studies of nine of these antidepressants (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone and mirtazapine) in youth populations. Of note, these medications were prescribed in trials not only for depression but also for anxiety disorders and ADHD. It is important to note that, among the 4400 patients treated with SSRIs or atypical antidepressants in these studies, there were no completed suicides. However, when evaluated together, the risk of “suicidality” (defined as suicidal thinking and behavior) in the antidepressant trials was approximately twice that of placebo: 4% vs. 2% respectively (risk ratio, 1.95; 95% CI 1.28-2.98), a finding that was supported by a recent reanalysis of largely the same studies (Wohlfarth et al., 2006). There was also a significant effect for treatment-emergent agitation or hostility (Hammad, 2006).

Of note, the above FDA analyses were based on adverse-event reports, an unsystematic and therefore unreliable method of obtaining data. Among the seventeen trials which utilized questionnaires to obtain data regarding suicidality, no evidence of medication-associated worsening of suicidality (risk ratio 0.92; 95% CI 0.76-1.11) or emergence of suicidality (risk ratio 0.93; 95% CI 0.75-1.15) was identified (Hammad, 2006).

When the FDA restricted its analysis to trials of major depression, statistically significant differences in suicidality and treatment emergent agitation or hostility persisted (Hammad 2004; see Table 7). Depressed youth treated paroxetine were most likely to experience treatment-emergent agitation or hostility (relative risk 7.69; 95% CI 1.80 – 32.99). Those

treated with venlafaxine XR were most likely to experience suicidality (relative risk 8.84; 95% CI 1.12-69.51).

Table 7

Published, Placebo-Controlled, Randomized Clinical Trials of SSRIs and Newer Antidepressants in Children and Adolescents

Drug	Suicide-Related Events		Treatment-emergent Agitation or Hostility	
	Relative Risk	95%CI	Relative Risk	95%CI
Nefazodone	No events	n/a	1.09	.53-2.25
Citalopram	1.37	.53-3.50	1.87	.34-10.13
Fluoxetine	1.53	.74-3.16	1.01*	.40-2.55
Mirtazapine	1.58	.06-38.37	0.52	.03-8.27
Paroxetine	2.15	.71-6.52	7.69	1.80-32.99
Sertraline	2.16	.48-9.62	2.92	.31-27.83
Venlafaxine SR	8.84	1.12-69.51	2.86	.78-10.44
Total	1.66	1.02-2.68	1.79	1.16-2.76

* FDA Analysis of treatment-emergent hostility or agitation did not include data from the TADS study; **Bold** = statistically significant result

Based on the above analyses, the FDA concluded that a true risk may exist for some youth. As a result, in October 2004 the FDA issued a “black box” warning alerting healthcare providers and consumers about “an increased risk of suicidal thinking and behavior (suicidality) in children and adolescents” who are taking antidepressant medication (FDA Website). The FDA review panel included all antidepressants in its warning due to concern that limiting the black box to newer agents would encourage the use of older medications with narrower therapeutic windows and higher lethality in overdose (Gibbons et al., 2005). In Dec 2004, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) Scientific Committee similarly advised that newer antidepressants “...are not authorized Europe-wide for the treatment of depression and anxiety disorders in children and adolescents. These compounds should generally not be used in this

age group because clinical trials have shown an increased risk of suicidal behavior...” (EMEA website: <http://www.emea.eu.int/>).

9.2.1.4 Investigations of Other Sources of Evidence

Given the problems inherent in drawing conclusions about suicidality from studies not designed or powered for such a purpose (Emslie et al., 2005), several pharmaco-epidemiological and observational studies have been undertaken in order to further examine the link between newer antidepressants and suicide or suicidal behavior.

9.2.1.5 Antidepressants and Completed Suicides

One frequently utilized pharmaco-epidemiologic technique involves investigating whether or not regional changes in rates of prescription of newer antidepressants are correlated with changes in suicide rates. Several of these large, retrospective studies have been completed (Gibbons et al., 2005; Hall et al., 2003; Helgason et al., 2004; Ludwig et al., 2005; Olfson et al., 2003; Sondergard et al., 2006). While one Australian study did identify a link between increased prescription rates of newer antidepressants and increased suicide rates in adolescents and young adults ages 15 to 24 (Hall et al., 2003), other American and international studies indicate an inverse relationship between rates of SSRI prescriptions and rates of suicide in child and adolescent populations (Gibbons et al., 2005; Ludwig et al., 2005; Olfson et al., 2003). According to an analysis of WHO data performed by the American College of neuro-psychopharmacology (ACNP) Task Force on SSRIs and Suicidal Behavior in Youth, over the past 14 years the suicide rate for adolescents and young adult (ages 15-24) has decreased by an average of 33% across 15 countries (Mann et al., 2006a). While such analyses are imperfect and subject to the “ecologic fallacy” (Robinson, 1950), taken together, these studies do not lend strong support to the notion that newer antidepressants are linked to increased rates of youth suicide.

In addition to pharmaco-epidemiologic studies, others groups have used post-mortem toxicological analyses as a means of investigating a link between completed youth suicide and antidepressant medications. Evidence from a large-scale Swedish study (Isacson et al., 2005a) and two smaller American studies (Moskos et al., 2005; Tardiff et al., 2002) does not support an association between treating youth with antidepressants and subsequent completed suicide.

9.2.1.6 Antidepressants and Suicidal Behavior or Non-Fatal Self Harm in Depressed Youth

In addition to completed suicides, information is also available regarding suicidal behavior and non-fatal self harm. Several retrospective studies have investigated this potential link through queries of large databases of patient information. The results of these studies are mixed.

In 2004, Valuck et al conducted a propensity-adjusted cohort study to examine links between antidepressant treatment and suicide attempts in over 24,000 adolescents (ages 12-18) who were started on antidepressants after being newly diagnosed with major depression. After adjusting for severity of symptoms, they found youth treated with SSRIs did not have statistically significant increases in rates of suicide attempts when compared to youth treated with other or multiple medications. Youth who continued treatment with any antidepressant for six months made significantly fewer suicide attempts than those who remained on medication for less than eight weeks. (Valuck et al., 2004).

Martinez et al conducted a nested case-control study comparing rates of fatal and non-fatal self harm for over 146,000 individuals in a large UK general practice database (Martinez et al., 2005). Identified cases were prescribed TCAs, SSRIs or atypical antidepressants for a depressive episode (unipolar or bipolar) or dysthymia. In the six-months following index prescription, no suicides occurred in the 10 to 18 year old cohort. However, compared to depressed youth treated with TCAs, depressed youth treated with SSRIs demonstrated “weak

evidence” for increased rates of non-fatal self harm (adjusted odds ratio 1.59; 95% CI 1.01 – 2.50). Among the SSRIs evaluated, the greatest risk for non-fatal self harm was associated with paroxetine. Jick and colleagues found a near-significant signal for increased rates of self-harm in paroxetine-treated youth (ages 10-19) in an earlier study of the same database (Jick et al., 2004).

In a separate study, Simon and colleagues used a large American database to retrospectively analyze over 82,000 index episodes of antidepressant treatment, 5107 of which involved youth ages 5 to 18 (Simon et al., 2006). Six months after initiating antidepressants diagnosed depressive disorders (coded as ICD-9 MDD, Dysthymia, or Depressive Disorder NOS), three youth and 28 adults completed suicide. Like Jick and colleagues, Simon and colleagues found a significantly higher rate of suicide attempt in the first week of treatment compared to subsequent weeks. However, when compared across the entire sample, there was not a statistically significant increased risk of completing suicide the first month of treatment compared to subsequent months. Additionally, rates of serious suicide attempts, captured from three months before to six months after index antidepressant prescription, were highest in the month before antidepressants were initiated. When the newer antidepressants included in the FDA review were compared to the older antidepressants not evaluated by the FDA, this decrease in suicide attempts in the month after treatment initiation was only seen with newer antidepressants. The authors state that these differences may reflect a more timely therapeutic effect of newer agents.

9.2.1.7 The use of antidepressants and its risks, benefits

Several recent studies have used metanalysis to compare the risks and benefits of individual antidepressant agents that have been subject to randomized clinical trials in depressed youth (Bridge et al., 2005; Wallace et al., 2006; Whittington et al., 2004). The authors of each of these studies conclude that the risk-benefit profile is most favorable for fluoxetine. Two of the

studies suggest that the risk-benefit profile of citalopram is also positive (Bridge et al., 2005; Wallace et al., 2006); one study suggest that the benefits of sertraline may also outweigh it's risks when used to treat depressed youth. Based on all of the preceding data, the following recommendations might be considered regarding diagnosis and treatment of youth with major depression.

- **Carefully diagnosis the patient.** Comorbidities or alternate diagnoses such as bipolar disorder may affect both safety and efficacy of drug treatment.
- After careful diagnosis, **discuss the risks and benefits of treatment** with antidepressants and/or psychotherapy. The discussion should involve the parent(s) or guardian(s) and, whenever appropriate, the patient. The conversation should reflect both the treatment-associated risks as well as the risk of untreated depression.
- If depressive symptoms are mild or if the current episode is of new or recent onset, **consider a period of intensive psychosocial therapy, support and monitoring.** Given the episodic nature of depression and the turbulence of youth, particularly adolescence, some depressive episodes may respond to psychotherapy, simple supportive interventions, or may even remit spontaneously. However, even if symptoms remit, patients should be considered at risk for future depressive episodes and receive regular monitoring. If symptoms worsen or persist for six to eight weeks, an evidence-based treatment with medication and/or a specific psychotherapy should also be initiated if only support has been offered up to that point.
- **Educate the patient and family about what to expect** from drug treatment. It is important to let them know that they may experience a drug's side effects before they experience the benefits. Provide them with information about irritability, akathisia, agitation and mania, and encourage them to call with questions. The Parent's Med Guide is one useful resource available on the world wide web (www.parentsmedguide.org) in English and Spanish.

- **Develop a safety plan** with the patient and the responsible adult. Both the child and parent/guardian should have numbers for the doctor/clinic as well as a plan for accessing emergency services. If the patient is experiencing suicidal ideation but is appropriate for outpatient treatment, provide only limited amounts of medication. Encourage parents to remove firearms or other dangerous equipment from the house.
- **When initiating medication, start low and monitor carefully.** While starting low, children may be able to tolerate and sometimes require similar doses as adults. Monitoring must be tailored to fit individual clinical situations. The FDA recommends the monitoring schedule listed below, which was also used in TADS study. Particularly in the initial weeks, in addition to monitoring for suicidality, patients and families should be asked about medication compliance and behavior change.
 - **Every week for the first 4 weeks**
 - **Every other week for the next four weeks**
 - **After twelve weeks, then as necessary**
- **If patient responds, treatment should continue.** “Continuation” treatment for 3-6 months after remission helps reduce rates of relapse. If children or adolescents have suffered previously from episodes of depression, a “maintenance” phase of one to three years should be strongly considered. If a medication discontinuation trial is desired after a period of sustained remission, it should be well-planned, slowly conducted, and carefully monitored.
- **If patient does not respond, re-evaluate diagnosis** before moving on to alternate drug strategy. If diagnosis is confirmed, try a different medication. While fluoxetine should be favored as a first-line antidepressant based on the above-described evidence and its FDA-indication, not all patients will tolerate or respond to this medication; if this is the case, other medications can and should be used.

9.2.1.8 Conclusion

While much is known about the effects of antidepressant medications in children and adolescents, research is needed to further improve our ability to treat depressed youth. The current evidence for efficacy is not robust, and several questions regarding the safety of newer antidepressants remain.

Regarding efficacy, more information is needed in order to determine which children and adolescents respond to which treatments. Current treatment studies have been characterized by high placebo response rates and sub-optimal response rates. Important questions regarding the effects of early intervention and long-term treatment in both children and adolescents also remain.

The debate over the safety of these medications will also continue. If the risk is determined to be real, investigators must identify an etiology of self-harmful or suicidal behavior, and conclude whether or not harmful these behaviors can be predicted and neutralized. Given the known morbidity and mortality associated with untreated depression, all risks of treatment must be balanced against the risk of withholding treatment. Regardless of treatment status, all depressed children and adolescents will require psychoeducation and careful monitoring.

9.2.2 Antidepressant Treatment in Old Age

9.2.2.1 *General clinical considerations*

The prevalence for depressive symptoms in people over the age of 65 ranges between 8 and 17% and between 1 and 3% for major depressive episodes (Mitchell et al., 2005). Moreover, a considerable co-morbidity exists with dementia, stroke and Parkinson's disease, where patients often present with depressive symptoms. The response to antidepressant treatment in the elderly does not apparently differ from treatment response in younger patients. However, relapse rates are higher and the longitudinal outcome is less favorable than in the middle ages (Mitchell et al., 2005). There are very few longitudinal studies following the course of depressive illness in elderly people. The meta-analysis of data from 12 studies in primary care and in community secondary care showed that after 2 years 21% of elderly depressed patients had died and among survivors almost half remained depressed (Mitchell et al., 2005). The more adverse longitudinal course in old age may be more likely accounted for medical co-morbidity, immobility and psychosocial factors (Mitchell et al., 2005) than age itself (Mitchell et al., 2005). It is also generally accepted, that elderly depressed patients are particularly prone to the side effects of antidepressants, particularly cardiovascular side effects and treatment related cognitive dysfunction (Moskowitz et al., 1986).

It also may be important to distinguish between young-old (age 60-75 years) and old-old (age over 75 years). Both groups show marked differences in co-morbidity (e.g. dementia), lifestyle and rates of institutional care. However, in most antidepressant trials this distinction has not been made and patient samples in previous studies are usually heterogeneous and termed as elderly, geriatric, senile or older adults, aged 55 or over (Mottram et al., 2006).

9.2.2.2 *Efficacy of antidepressants in old age*

Numerous randomized controlled trials of antidepressant treatment in late-life depression have been conducted including all substance classes. The first question is whether antidepressant pharmacotherapy is effective at all in elderly patients, i.e. shows therapeutic efficacy superior to placebo treatment. Roose and Schatzberg (Roose et al., 2005) recently reviewed five placebo-controlled which have been selected based on quality criteria in order to assess the antidepressant efficacy and effectiveness. Useful data on TCAs are very limited because previous studies have often involved inadequate dosages of TCAs (e.g. imipramine and amitriptyline), which are not recommended for the use in elderly patients (Mamdani et al., 2000b). Thus, four of these randomized controlled trials (Rapaport et al., 2003; Roose et al., 2004; Schneider et al., 2003; Tollefson et al., 1995) compared different SSRIs (fluoxetine, sertraline, citalopram, paroxetine) and one trial fluoxetine and venlafaxine with placebo (Schatzberg et al., 2002). Three studies demonstrated a statistically difference in drug versus placebo response and/or remission rates (Rapaport et al., 2003; Schneider et al., 2003; Tollefson et al., 1995). The percentage of trials failing to show a significant difference between verum and placebo groups resembles results of non geriatric trials, where medication is found to be more effective than placebo in less than 50% of the time. In 1999 the World Psychiatric Association (WPA) recommended among general medical principles to treat depressive symptoms in the elderly with the aim of complete remission. A more recent guideline of a working group of the Royal College of Psychiatry from UK (Baldwin et al., 2003) supported also the efficacy of antidepressant drugs in elderly patients based on a previous Cochrane Review (Wilson et al., 2001) and further meta-analysis (Gerson et al., 1999; McCusker et al., 1998; Mittmann et al., 1997). In contrast, little is known about augmentation strategies in elderly patients who have shown only modest improvement during previous treatment trials (Baldwin et al., 2003).

Another question is whether a certain class of antidepressants is more favorable in old age than the others. Roose and Schatzberg (Roose et al., 2005) also selected 6 trials comparing at least two different antidepressants for further critical review. All randomized controlled trials in this review were comparison trials of two SSRIs or one SSRI compared to a TCA or mirtazapine (Bondareff et al., 2000; Mulsant et al., 2001; Navarro et al., 2001; Newhouse et al., 2000; Roose et al., 2004; Schatzberg et al., 2002). The response rates in these comparison trials were consistently higher than seen with the same agents in placebo-controlled trials (50-73% vs. 35-72%) and may better reflect the effectiveness of medication in a clinical setting (Roose et al., 2005). These trials did not demonstrate that one antidepressant is superior to another. In a very recent Cochrane-Analysis (Mottram et al., 2006) 29 studies out of 163 identified trials were selected for further analysis and 14 studies were selected for contributing efficacy data. Trials entering the meta-analysis of efficacy had to compare at least 2 active antidepressant drugs as the meta-analysis aimed at comparing the efficacy of antidepressant classes, withdrawal rates and side effect profiles in elderly patients. The trial duration varied between 4 and 8 weeks and only 2 trials (comparison of moclobemide with imipramine and tianeptine) were conducted over 12 weeks or more (Dunningham et al., 1994). No significant differences in efficacy were found between classes of antidepressants (TCAs, TCA related drugs, SSRIs, MAOIs and atypical antidepressants). However, the trials contained relatively small numbers of patients possibly introducing a large type two error which may explain the negative finding. Higher numbers of patients withdrawn irrespective of reason or due to side effects were observed during treatment with TCAs compared to SSRI. Also ECT has been shown to exert excellent effectiveness in geriatric patients (Abrams, 2002; Greenberg et al., 1992; Oshima et al., 1999). Despite specific side effects such as greater cognitive impairment, efficacy is greater in older than in younger patients and a reduced mortality in comparison to other treatments has been shown (Philibert et al., 1995). Further progression in understanding of ECT and anesthesia has reduced the risks of ECT. So no

absolute medical contraindications to its use, particularly in patients at particular medical risks, are encouraged now (Abrams, 2002; Fink, 1999) enabling psychiatrists to offer a growing proportion of geriatric patients ECT treatment.

9.2.2.3 Tolerability in elderly patients

The recent Cochrane analysis (Mottram et al., 2006) of side effects showed an small increased risk of gastrointestinal (including the experience of “dry mouth”) and neuropsychiatric side effects (drowsiness, dizziness, lethargy) associated with classical tricyclic antidepressants. However, further conclusions regarding the comparison of other substance classes have not been possible due to the methodological limitation mentioned above. Thus, only the pharmacological profiles of specific drugs and their interactions with medical comorbidity and concomitant medication can determine the choice of antidepressants in elderly patients. In primary care, newer drugs providing a superior safety profile such as SSRIs are gradually replacing TCAs as first-line treatment based on their superior side effect profile (Gareri et al., 1998; Mamdani et al., 2000a). Moreover, geriatric patients are more susceptible to side effects such as orthostatic hypotension and sedation. Also cognitive disturbances and even delirious states induced by the anticholinergic action of various antidepressants, e.g. TCA, are more frequent. Some side effects, which raise particular concerns in younger patients such as weight gain due to antihistaminergic effects, may be beneficial for elderly patients often suffering from anorexia and weight loss. In existing medical co-morbidity, which may complicate the management of late-life depression, particular care should be paid in choosing an antidepressant. According to the guidelines from UK (Baldwin et al., 2003) SSRIs should be preferred for depression complicating vascular and cerebrovascular disease, mainly because of safety and tolerability. In dementia tricyclic antidepressants, SSRIs and moclobemide are effective, however, newer drugs are better tolerated and safer. For

Parkinson's disease no adequate trial data is available, however, SSRIs may aggravate parkinsonian symptoms, but this has not been proven (Baldwin et al., 2003).

9.2.2.4 Dosage and duration of antidepressant treatment in old age Comorbid medical conditions and concomitant medications require particular attention to pharmacodynamic and pharmacokinetic interactions. Even if no other medical disturbances are present, normal aging leads to differences in hepatic and renal function requiring extraordinary awareness. Because of a reduced hepatic metabolism and renal elimination rate in the elderly the appropriate dosages are lower than in younger patients (Chiu, 1997). In frail patients it is recommended to commence treatment with a slow dosage and titrate gradually to the therapeutic dosage range ("start low and go slow"). Moreover, the guidelines of the American Psychiatric Association (APA) emphasize that elderly patients typically require a lower dosage than younger patients to reach a particular blood level and tolerate a given blood level less well, however, the blood levels at which antidepressant medications are maximally effective appear to be the same as for younger patients (American Psychiatric Association, 2000; Wilson et al., 2001). Another critical issue is the duration of treatment in old age. Apparently older patients take longer to recover from depression and recovery goes on up to 12 weeks provided that there has been some early improvement (Wilson et al., 2001). Currently at least 6 weeks of treatment is recommended to achieve optimal therapeutic effects (Wilson et al., 2001). However, if there has been hardly any response (e.g. less than 25% recovery) during the first four weeks the same treatment is associated with a low probability of remission (Mottram et al., 2006). After remission antidepressant medication at the same dose should be continued for another 12 months in first-onset cases and up to 36 months in recurrent cases (Nemeroff et al., 1984).

10 Mechanisms of action of antidepressants

10.1 The development of antidepressants based on the monoamine hypothesis of depression.

Following the accidental discovery of the monoamine oxidase inhibitors and the tricyclic antidepressants some 50 years ago (Slattery et al., 2004), the pharmaceutical industry developed numerous antidepressants that had similar therapeutic and adverse side effects. The observation that imipramine reduced the transport of tritiated noradrenaline and serotonin into rat brain slices in vitro, whereas iproniazid, the first clinically effective MAOI, inhibited the intraneuronal metabolism of these biogenic amines, gave support to the emerging monoamine hypothesis of depression. However, despite the refinement of the pharmacology of the antidepressants that led to the synthesis of drugs that were highly selective in blocking either the reuptake of noradrenaline (the noradrenaline reuptake inhibitors, NRIs, as exemplified by maprotiline and reboxetine) or serotonin (the selective serotonin reuptake inhibitors, SSRIs, as exemplified by fluoxetine) (Brunello et al., 2002; Nutt, 2002), it soon became apparent that not all antidepressants blocked the monoamine transporters. Indeed, mianserin, a tetracyclic compound, was the first effective antidepressant that had no effect on either the monoamine transporters or monoamine oxidase but was an effective antidepressant. Later it was found that the tetracyclic antidepressant mianserin had a unique mode of action in that it increased the release of noradrenaline by blocking the pre-synaptic, inhibitory, α_2 adrenoceptors. As these receptors, on stimulation by inter-synaptic noradrenaline, normally reduce the influx of calcium ions and thereby reduce the calcium dependent release of noradrenaline, drugs that specifically block the pre-synaptic α_2 receptors would be anticipated to increase the intraneuronal concentration of calcium and thereby increase noradrenaline release. This is how mianserin was thought to act. More recently mirtazapine, a structural relative of mianserin, has been developed that combines the enhanced release of noradrenaline with an

increased activation of post-synaptic 5HT_{1A} receptors and an antagonism of 5HT₂ and 5HT₃ receptors. Thus, a slight modification of the tetracyclic structure of mianserin has led to the development of a dual action antidepressant that lacks the gastrointestinal and neurological side effects of the SSRIs, adverse effects that are the result of the activation of serotonin receptors (5HT_{2C}, 5HT₃) in the gastrointestinal tract and on blood vessel walls. It is interesting to note that following two decades of emphasis of specificity of action of antidepressants on noradrenaline, serotonin or even dopamine (for example, bupropion), there is now a renewed interest in antidepressants with a dual action, in other words, tricyclic-like antidepressants that lack the cardiotoxicity and other adverse side effects. Venlafaxine and duloxetine are examples of monoamine reuptake inhibitors that, at normal therapeutic doses, show a greater potency in inhibiting serotonin rather than noradrenaline reuptake whereas milnacipran is more selective in inhibiting noradrenaline reuptake at normal doses. These dual action antidepressants (Briley, 1998) enhance both noradrenaline and serotonin at high therapeutic doses whereas mirtazapine, because of a different mode of action, does so across the therapeutic dose range.

Recent developments also show important differences between different subtypes of SSRIs. E.g. Escitalopram, binding to both the primary binding site and to the allosteric site on the serotonin transporter, seems to be different from other SSRIs (Chen et al., 2005; Sanchez et al., 2004; Thase, 2006).

Despite the plethora of different types of antidepressants that have been marketed over the past 30 years (**Fehler! Verweisquelle konnte nicht gefunden werden.**, for review see (Richelson, 2001)), the main advance has been made not in terms of efficacy but safety. Modern antidepressants are no more effective than the first tricyclics such as imipramine or amitriptyline. Indeed, electroconvulsive therapy (ECT) remains the most effective and reliable means of treating severe depression (ECT review group, 2003).

Table 8

Selection of antidepressants that are currently available in Europe (see Table 9 for a more detailed list)

Selective serotonin reuptake inhibitors (SSRIs)	citalopram escitalopram fluvoxamine fluoxetine sertraline paroxetine
Serotonin reuptake activators	tianeptine
Selective noradrenaline reuptake inhibitors	reboxetine
Selective noradrenaline and serotonin reuptake inhibitors	venlafaxine duloxetine milnacipran
Noradrenaline and serotonin specific antidepressants	mirtazapine
α_2-adrenoceptor antagonists	mianserin
5HT₂ receptor antagonists	nefazodone trazodone
Reversible inhibitors of MAO	moclobemide toloxatone
Dopamine and noradrenaline reuptake inhibitor	bupropion
5HT_{1A} agonists *	ipsapirone gepirone
5HT_{2C} antagonist + melatonin-1 agonist *	agomelatine

*Not yet marketed in Europe

While it is generally assumed that all effective antidepressants enhance monoaminergic function in some way, their common mode of action remains an enigma. It has long been realized that there was a disparity between the qualitative and quantitative effects of these drugs on monoamine transport and the onset of their therapeutic action (Nestler, 1998). In addition to the delay in the onset of the therapeutic action, the acute depletion of tryptophan from the diet, an event that significantly decreases the concentration of brain serotonin, results in either no effect or a mild dysphoria in healthy volunteers and does not affect the mood state of untreated depressed patients (Delgado, 2004; Nestler, 1998). Nevertheless tryptophan

depletion is able to acutely reverse the therapeutic actions of chronic SSRI treatment and to cause acute relapse in recovered unmedicated patients (Bell et al., 2001). These effects show that in vulnerable individuals acute lowering of 5-HT function can contribute to depressive states.

The discovery that chronic antidepressant treatment produces adaptive changes in postsynaptic beta-adrenoceptors that approximately correlated with the onset of the antidepressant effect (Sulser et al., 1978) opened up a new concept regarding the mode of action of antidepressants by directing research away from presynaptic to postsynaptic events. It soon became apparent that the changes in postsynaptic monoamine receptors were coupled to changes in intracellular signal transduction molecules. This stimulated research into the effects of chronic antidepressants on neuropeptides, neurotrophic factors and intracellular signaling molecules (Manji et al., 2001; Wong et al., 2004b). A variety of recent studies supported the hypothesis that possibly a decreased expression of brain derived neurotrophic factor (BDNF) contributes to the development of depressive disorders and that upregulation of BDNF plays a role in the actions of antidepressant treatments (Duman et al., 2006). Thus, the monoamine hypothesis of depression, and the explanation of how antidepressants work, has gradually evolved into a molecular hypothesis. This is based on the view that adverse environmental factors, such as stress, acting on a genetic vulnerability, cause maladaptive changes in a range of neurotransmitters of which the monoamines are presumed to play a significant role. Effective antidepressant treatments normalize the disturbed neurotransmitter networks that are assumed to be responsible for the clinical features of depression (Castren, 2005). This hypothesis has stimulated the search for genes that are altered in depression or by chronic antidepressants in the hope that the molecules encoded by these genes could provide targets for novel types of antidepressants (Knuuttila et al., 2004; Wong et al., 2004a).

10.2 New developments leading to a new understanding of the mechanism of action of antidepressants

Despite the advances that have been made in the treatment of depression over the past 50 years, a number of major problems remain. These include a lack of response, or only a partial response, to treatment by a substantial proportion of patients. In addition, the diagnosis of depression, and the different types of depression, is dependent on the symptoms; these are frequently complicated by co-morbidity with other psychiatric disorders. Clearly the development of specific diagnostic tests for depression would be a major advantage but, to date, no such tests have been reliably developed. It would also be a help if there were reliable animal models of depression but, again, those that are available have been of limited value for the detection of novel compounds or in elucidating the mechanisms whereby antidepressants work. Some of these issues have been discussed elsewhere in this document. Most animal models of depression rely on stress-induced abnormalities in behavior and in the subsequent changes in neuroendocrine and neurotransmitter (mainly monoamine) function. It has been more recently reported alterations in the expression of numerous genes and notably those coding for neurotrophic factors such as BDNF and NGF (Alfonso et al., 2006) as well as structural modifications in the areas of the brain related to mood disorders in animal submitted to such paradigms. This has led to depression research being focused on the hippocampus, amygdala, cortex and related neuronal circuits (LeDoux, 2000). The importance of these regions has gained support from brain imaging studies which have identified many cortical and subcortical structures that are altered in depressed patients. These observations are completed by those from post mortem studies: in the same regions, alterations of both neurons and glial cells density and size seem affected, suggesting a functional impairment of these regions associated with major depression (for review see (Gould et al., 2004)). Furthermore effective antidepressant treatments have also identified the importance of these brain regions (Tamminga et al., 2002).

Clearly the application of neuroscience to an understanding of brain function and psychopathology has resulted in novel insights into the psychobiology and biological subtypes of depression (Hasler et al., 2004) and, possibly, how antidepressants work. This raises the question “Is mood chemistry?”, the subject of an important review by Castren (Castren, 2005). This new concept suggests that depression results from a malfunction of neuronal networks and that antidepressants work by improving information processing in the affected networks. At the basis of such disordered networks lies the failure of neuroplasticity. Thus, all antidepressants appear to increase the development of new neurons in the hippocampus (Malberg et al., 2000). This increase in neurogenesis in the hippocampus associated with chronic antidepressant treatment correlates with the behavioral changes caused by chronic antidepressant treatments (Santarelli et al., 2003). It should be highlighted that numerous other alterations than a decrease in the rate of neurogenesis or in neuronal turnover in the hippocampus have been reported in depression such as modifications in neuron architecture, only few publications have reported the effect of antidepressants on them. Such observations are particularly pertinent to the mode of action of antidepressants as, for the first time, a cellular explanation has been proposed that identifies the reason for the delay in the onset of the response to treatment independently of the nature of that treatment. This hypothesis has led to the further observation that the elimination of neurons through apoptotic cell death increases simultaneously with increased neurogenesis, events that are linked to the antidepressant-induced increase in neurotrophic factors such as brain-derived neurotrophic factor (BDNF). It may be hypothesized that, in the hippocampus, antidepressants increase neuronal turnover rather than neurogenesis per se (Sairanen et al., 2005). What are the implications of such findings for the development of future antidepressants? Clearly the conventional approach whereby specific monoamine neurotransmitters are targeted must be reconsidered. It can be argued that such an approach has failed to bring about any major benefits to the depressed patient in terms of therapeutic efficacy. Further targets,

while they may include monoamine receptors such as the 5HT_{2A}, 5HT_{2C}, 5HT₆ and 5HT₇ (Pauwels, 2000), have certainly produced some potentially interesting possibilities in rodent models of depression but so far they have not yet been validated clinically. There is evidence that 5HT_{1A} and 5HT_{1B/D} antagonists augment the antidepressant response, but the clinical evidence that such drugs are effective antidepressants when administered alone is equivocal (Bosker et al., 2004). Similarly, the α_2 adrenoceptor has been targeted following the discovery that the tetracyclic antidepressants mianserin and mirtazapine act as antagonists at the pre-synaptic α_2 receptor (Blier, 2001) and block certain 5-HT₂ receptors. Therefore both drugs are influencing the noradrenergic and serotonergic neurotransmission.

Recently it has been shown that a peptide that is a member of the S100 interacts with the 5HT_{1B} receptor; there is experimental evidence that the function of this receptor is dependent on the expression of the p11 peptide (Sanacora et al., 2000). The concentration of the p11 peptide was shown to be low in post-mortem brains from depressed patients. In knockout mice lacking the p11 peptide, depressive-like behavior was noted. Chronic antidepressant treatments, including ECT, increased p11 expression and counteracted the depression-like phenotype (Svenningsson et al., 2006). These results serve to emphasize the potential importance of the 5HT_{1B} receptor in animal models for depression and suggest 5HT_{1D} receptors, the analogous serotonin receptor in man may play a role in antidepressant therapies. Non-monoamine approaches have included antagonists of tachykinin receptors. The endogenous agonists include the peptide Substance P that is physiologically involved with pain perception, but experimental studies have demonstrated that NK1 receptors may function to modulate serotonergic transmission (Santarelli et al., 2001). Antagonists of these receptors would therefore be expected to exert the opposite effect upon serotonergic transmission and enhance function (Culman et al., 1997). While there was considerable excitement generated regarding the antidepressant potential of the first NK1 antagonist to be developed some years ago (Schwarz et al., 2002), further clinical studies have proved disappointing. Nevertheless, of

the 5 known types of the NK receptors the search continues for antagonists with potential therapeutic properties (Kramer et al., 1998).

Of the amino acid neurotransmitters, attention has been directed to the N-methyl-D-aspartate (NMDA) receptor complex following experimental findings that have shown that most classes of antidepressants decrease the affinity of the glycine site on the NMDA receptor complex (Grundemar et al., 1994) following chronic antidepressant treatment. This may prove to be a novel approach to drug development, as the NMDA antagonist ketamine has been shown to cause a rapid, but transient, improvement in mood in depressed patients (Paul et al., 1994). At the cellular level, NMDA antagonists block the atrophy of hippocampal CA3 pyramidal neurons and the inhibition of neurogenesis caused by stress (Berman et al., 2000a). Another possible approach to the modulation of the glycine site on the NMDA receptor involves sigma receptor antagonists. Ipmesine was the first sigma-1 receptor antagonist that was shown to have antidepressant activity (Manji et al., 1999; Roman et al., 1990), but for commercial reasons it has not been developed. The antidepressant tianeptine has demonstrated to counteract the stress-induced increase in NMDA/AMPA ratio (Kole et al., 2002). Of the other amino acid receptors that are possible targets the observation that the concentration of GABA is decreased in the brains of depressed patients (Sanacora et al., 2000) suggests that GABA receptor agonists, particularly those targeting the G-protein coupled GABA-B receptor that are prominently located in limbic regions of the brain, may be of interest. For a detailed review of new hypotheses on antidepressant modes of action see (Slattery et al., 2004).

10.2.1 HPA system abnormalities in depressive disorders

A dysregulation of the HPA system is one of the major neuroendocrine abnormalities in major depressive disorder including elevated levels of CRH (Nemeroff et al., 1984), ACTH, and cortisol (Linkowski et al., 1987) during depressive episodes, which normalize after clinical

remission. Higher HPA activity during the first weeks of an antidepressant pharmacotherapy seems to be associated with lower rates of early treatment response (Hatzinger et al., 2002). Furthermore it is of importance that persisting cortisol hypersecretion indicates a higher risk for the recurrence of depression, even if a reduction of depressive symptoms or even clinical remission has been achieved (Zobel et al., 1999). Moreover during the long-term course of depression an increasing HPA system deterioration is highly correlated not only with the severity of disease, indicated by higher psychometric depression scores, but also with the number of previous episodes (Hatzinger et al., 2002). However, in both molecular investigations and animal studies it has been shown that classical antidepressants, e.g. tricyclic antidepressants, modulate the regulation of the HPA system by enhancement of the expression of glucocorticoid receptors thereby improving the feedback mechanism of the HPA system (Barden et al., 1995; Holsboer et al., 1996). Thus, the regulation of the HPA system seems to play a major role for the pathophysiology of depressive episodes. This neuroendocrine regulatory system therefore opens a variety of new pharmacotherapeutic approaches to depression which differ fundamentally from up to now available antidepressants.

The HPA and immune axis has become an important target for antidepressant development due to the key role that stress plays in initiating depression. In the development of novel drugs that target the HPA axis, one approach has involved antagonists of the CRF1 receptors. Clinical studies have shown that the concentration of CRF is increased in the CSF of both suicide victims and in depressed patients (Nemeroff, 1996). However, in spite of first clinical experiences supporting a potential antidepressant efficacy, so far CRF antagonists have not shown their efficacy in the treatment of depression in RCTs. More success has been reported in the development of glucocorticoid type-2 receptor antagonists. This approach was based on the observation that hypersecretion of cortisol is a frequent occurrence in patients with chronic depression in which melancholic features are prominent. There is preliminary clinical

evidence that novel glucocorticoid receptor antagonists may be beneficial in such subgroups of depressed patients (Gallagher et al., 2006).

A novel antidepressant, agomelatine, has been developed recently. It acts as an agonist at melatonin-1 receptors and as an antagonist at 5HT_{2C} receptors (Millan et al., 2003; Millan et al., 2005; Pevet, 2002; Scamps-Francois et al., 2003). Melatonin is secreted from the pineal gland and, via the supra-chiasmatic nucleus in the hypothalamus, acts as the endogenous circadian rhythm oscillator. As circadian rhythms are known to be altered in depression (Darcourt et al., 1992), it has been hypothesized that a drug acting as an agonist at melatonin receptors, and as an antagonist at 5HT_{2C} receptors that have been implicated as being oversensitive in anxiety and depression, could facilitate a resynchronization in circadian rhythms and have useful therapeutic properties (Krauchi et al., 1997; Leproult et al., 2005). The close inter-relationship between the endocrine and the immune system has stimulated research into the role of pro-inflammatory cytokines in the etiology of depression. Thus the observation that inflammatory mediators, such as the pro-inflammatory cytokines interleukin-1 and -6, tumor necrosis factor- α , interferon- γ and prostaglandin E₂, are elevated in the blood of depressed patients has led to the macrophage hypothesis of depression (Smith, 1991). In addition, the treatment of non-depressed persons suffering from hepatitis with interferon- α often results in severe depression (Wichers et al., 2002). Furthermore, many of the symptoms that occur in depression (for example, the sleep profile, mood, memory, appetite, libido, cognitive function, endocrine function) may also be caused by pro-inflammatory cytokines that are increased in the blood and CSF of depressed patients (Dantzer, 2004). Conversely, chronic treatment with antidepressants attenuates the release of pro-inflammatory cytokines from activated macrophages both in the blood (Xia et al., 1996) and in the brain (Obuchowicz et al., 2006). This suggests that antagonists of pro-inflammatory cytokines, and possibly cyclo-oxygenase-2 inhibitors that reduce the synthesis of prostaglandin E₂ in the brain, could act as novel antidepressants (Leonard, 2001). There is

some clinical evidence that cyclo-oxygenase inhibitors have antidepressant-like activity (Collantes-Estevez et al., 2003).

Whereas neurotransmitter receptors would appear to be the most accessible targets for the development of new antidepressants, there is now considerable research interest in intracellular signal transduction mechanisms which are targets for neurosteroids, neurotrophic factors and enzymes that are linked, directly and indirectly, to post-synaptic receptors that reflect the actions of both neurotransmitters and other physiologically active molecules such as the cytokines. To date, only one drug has been developed that appears to act by inhibiting a component of the post-receptor signaling system, rolipram, a phosphodiesterase inhibitor that is presumed to act by inhibiting the breakdown of the second messengers cyclic adenosine and guanosine monophosphates. As a consequence, the post-synaptic response to receptor stimulation is increased. In future, it seems likely that other post-synaptic targets will be investigated including mitogen-activated protein (MAP) kinase agonists that indirectly increase the synthesis of BDNF, a key neurotrophic factor for repairing damaged neurons (Altar, 1999). Other possible targets include protein kinase C (PKC), an enzyme involved in the regulation of neuronal excitability, neurotransmitter release and long-term synaptic events (Manji et al., 1999). Finally, in view of the importance of mechanisms that reduce apoptosis, and thereby assist in neurogenesis, antidepressants may be developed that act as promoters of anti-apoptotic proteins such as Bcl-2. This protein attenuates apoptosis by sequestering the pro-apoptotic caspase enzymes (Altar, 1999).

In conclusion, there are many possibilities for the future development of antidepressants. Microarray technology should enable candidate genes to be identified and targeted and undoubtedly such methods will play an increasingly important role in drug discovery in the future. However, it seems that the more conventional approach involving the identification of malfunctioning neurotransmitters and their signaling systems, and correcting their defects with novel molecules, offers the greater chance of success in the immediate future.

10.3 The role of pharmacogenetics in the understanding of how antidepressants work

Pharmacogenetics, a term proposed by Vogel in 1959, is the study of genetically based, inter-individual variability in response to drugs and their side-effects. It is now realized that polymorphisms of the cytochrome P 450 microsomal oxidase system in the liver is responsible for many of the genetic differences that affect drug responsiveness and metabolism.

An important area that is related to pharmacogenetics is pharmacogenomics. Whereas pharmacogenetics is concerned with the individual patient and how differences in metabolism and drug response are a reflection of the genetic make-up, pharmacogenomics is involved in the structure of the genome and how the targeting of compounds to the genome may lead to novel drugs that can be used to treat specific psychiatric disorders.

Classical genetics of human disease concentrate on monogenic disorders in which a single mutation or gene is the cause of the disorder. However, complex medical disorders such as diabetes, coronary artery disease and hypertension, and psychiatric disorders, are polygenic and therefore influenced by multiple factors that involved the genetic substrate and the environment.

Recent research has tended to focus on genes encoding for neurotransmitter receptors together with the enzymes that are involved in monoaminergic transmission. So far, the results of the studies have been equivocal in their findings with multiple claims for gene associations that could not be replicated. The limitations of the studies include the small sample sizes coupled with the small magnitude of the genetic effect. Nevertheless, the application of meta-analyses have identified several genetic variants of candidate genes. In bipolar disorder for example, a variant of the MAO-A gene has been identified (Furlong et al., 1999) although other investigators have been unable to confirm this finding (Schulze et al., 2000)

There have been several studies of the promoter polymorphism of the serotonin transporter gene. The type of polymorphism is functionally important as it appears that there is an association between depression and anxiety and the short allele (Lesch et al., 1996) However, once again, not all investigators have been able to replicate this finding (Serretti et al., 1999). Polymorphisms of other receptors and enzymes of the biogenic amines have also been investigated. These include the tyrosine and tryptophan hydroxylase genes, the catechol-O-methyl transferase gene as well as genes for the serotonin and dopamine receptors (Kato, 2001) To date these studies have yielded inconclusive or negative results. The conventional view that unipolar depression is under the control of the same genes irrespective of the age of onset of the disorder has been challenged by studies on late-onset depression (Hickie et al., 2001) Thus Hickie et al. (Hickie et al., 2001) have shown that late-onset depression is associated with a mutation in the methylene tetrahydrofolate reductase gene that controls an important co-factor in monoamine biosynthesis; this mutation was not found in patients whose depression occurred at an earlier stage. It appears that this same mutation predisposes the patient to cerebrovascular disease and is associated with increased plasma homocysteine and folate deficiencies that frequently occur in late-onset depression. Such observations serve to emphasize the difficulties that exist in attempting to identify specific genetic factors that may predispose to depression.

There are only a few small studies published in which pharmacogenetics has been used to predict therapeutic response in individual patients. These studies have investigated variations in the serotonin receptors (Lesch et al., 2004), serotonin transporter and their promoter, and their associations with a poor response to treatment with SSRI antidepressants (Joyce et al., 2003; Zanardi et al., 2001). Again, other investigators have been unable to replicate the observations that these parameters are associated with a poor antidepressant response (Kim et al., 2000). For a more extensive update on recent findings, we refer to recently published

reviews on pharmacogenetics and pharmacogenomics (Holsboer, 2001; Kirchheiner et al., 2004; Malhotra et al., 2004; Mancama et al., 2003; Serretti et al., 2005). Despite the current lack of knowledge of susceptibility genes for depression, it seems unlikely that this will discourage further research aimed at identifying the genetic basis of mood disorders by the application of DNA genotyping and genome-wide case controlled studies (Risch, 2000).

11 Pharmacological acute phase treatment options

11.1 Introduction and general information about antidepressants

Treatment of depressive disorders consists of a combination therapy which is determined by the current state of the illness. The main constituents of a multimodal antidepressant therapy are pharmacotherapy, psychotherapy, and sociotherapy. Whereas pharmacotherapy is not always mandatory for less severe forms of depression, severe depression usually requires pharmacotherapy or electroconvulsive therapy (ECT). The discovery of tricyclic antidepressants (TCAs) was a milestone in the treatment of depression. However, in spite of the undoubted effectiveness of tricyclic antidepressants it soon became apparent that they are somewhat problematic due to their inherent side effect profile. Particularly anticholinergic and antihistaminergic side effects cause considerable problems. As a consequence new antidepressants were developed with a more selective mode of action, which mainly aimed at avoiding these side effects. Due to historical developments the currently available antidepressants are usually classified according to their chemical structure and their mode of action. Whereas it seems plausible to maintain the classification according the chemical structure to separate TCAs and tetracyclic antidepressants from modern substances to describe safety and tolerability properties and to follow widespread habits, there seems to be no theoretical use for such a classification in evolving treatment plans and algorithms. A classification according to the predominant mode of action which is already in use concerning modern antidepressant substances seems to be more plausible and useful. Therefore we suggest to describe differential classes of modern antidepressants according their main mode of action, and to subdivide the older tri- and tetracyclic substances according their predominant influence on serotonergic and noradrenergic neurotransmission. Currently, tri- (TCAs) and tetracyclic antidepressants with predominant serotonergic (S-TCA), noradrenergic (N-TCA) or mixed (S/N-TCA) serotonergic/noradrenergic action are

available. To achieve sufficient simplification for more practicable treatment plans, tri- and tetracyclic antidepressants are summarized within the TCA group. In addition selective and reversible inhibitors of the monoamine oxidase A (RIMA), an irreversible MAO-B inhibitor (MAOBI), non-selective and irreversible inhibitors of the monoamine oxidase (MAOI), selective serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors (NARI), and antidepressants with a dual mode of action such as selective serotonin and noradrenaline reuptake inhibitors (SNRI), and noradrenergic and specific serotonergic antidepressants (NaSSA) acting via blockade of α_2 - and 5-HT₂-receptors are on the market (Blakely, 2001; Frazer, 2001; Kent, 2000; Pacher et al., 2001; Stahl, 1998). In addition a dopamine and noradrenaline reuptake inhibitor (DNRI) and serotonin modulating antidepressants (SMA) are available. The latest new developed mechanism of action is the agonism at melatonergic MT₁ and MT₂ receptors and selective antagonism at serotonergic 5-HT_{2c} receptors represented by the antidepressant agomelatine (MASSA) (Millan et al., 2003), which should get approval from authorities in Europe during 2006.

In general antidepressants, such as fluoxetine, trimipramine, Mirtazapine, mianserine, venlafaxine or reboxetine, are marketed as racemic compounds. As it can be observed in the case of citalopram and escitalopram both the pharmacological and the pharmacokinetic profile of these substances may differ between the enantiomers (Baumann et al., 2001; Baumann et al., 2002).

A consistent trend towards an increased use of generic antidepressants during the last years has been reported (Bruck et al., 1992). In general it has been supposed that original brand name antidepressants and generic substances exert similar efficacy and tolerability, but data are lacking whether this is true in each country. Direct comparisons between brand name formulations and generics and between different generic substances have not yet been published. And in addition it remains unclear whether pharmacogenetic differences in

populations of different countries may play a major role during clinical trials investigating those possible differences in efficacy and tolerability.

A summary of commonly used antidepressants including their primary mode of action and their additional influence on other receptor systems is shown in Table 9.

Table 9

Commonly used antidepressants⁴ including their primary mode of action and their additional influence on other receptor systems.

Primary mode of action	Generic name	Secondary mode of	Additional mode of action	Starting dose (mg)	Usual standard dose
SSRI	Citalopram			20	20-60
SSRI	Escitalopram	all. 5HTT ⁵		5-10	10-20
SSRI	Fluoxetine			20	20-80
SSRI	Fluvoxamine			50-100	100-300
SSRI	Paroxetine		(M ₁)	20	20-60
SSRI	Sertraline		DRI	50	50-200
SNRI	Venlafaxine			75	75-375
SNRI	Duloxetine			30-60	60-120
SNRI	Milnacipran			50	100-200
NARI	Reboxetine		(M ₁)	4	8-12
(NARI)	Viloxazine			100	200-500
NaSSA	Mirtazapine	5-HT _{2,3} , +5-HT	H ₁ , α ₁ , α ₂	15	30-45
MASSA	Agomelatine ⁶	5-HT _{2c}		25	25-50
RIMA	Moclobemide		(M ₁)	150-300	300-600
MAOBI	Selegiline ⁷			5-10	10
MAOI	Phenelzine			15	30-90
MAOI	Isocarboxacid			20	20-60
MAOI	Tranlycypromine			10	20-40

⁴ St. John's Wort is not included in the list of antidepressants because of no proven efficacy in severe depression

⁵ Additional binding to the allosteric site on the serotonin transporter. The definition of a new class of SSRIs has been suggested (Allosteric Serotonin Reuptake Inhibitors - ASRI)

⁶ Not yet available, FDA and EMEA approval expected during 2006.

⁷ Selegiline in some countries only has been approved as a drug against Parkinson's disease, not as an antidepressant

Primary mode of action	Generic name	Secondary mode of	Additional mode of action	Starting dose (mg)	Usual standard dose
SMA	Nefazodone	5-HT _{2a} SRI		100	300-600
SMA	Trazodone	5-HT ₂ SRI	α_1	50-100	200-600
DNRI	Bupropion	NRI		100	200-300
DNRI	Amineptine	NRI		100	200-300
DA	Trimipramine	5-HT ₂	H ₁ , M ₁ , α_1 , α_2	25-50	150-400
S-TCA	Tianeptine	SRS		12.5	25-37.5
S-TCA	Clomipramine	NRI, D ₂	M ₁ , α_1	25-50	100-250
S/N-TCA	Amitriptyline		H ₁ , M ₁ , α_1 , α_2	25-75	150-300
S/N-TCA	Amitriptylinoxid		H ₁ , (M ₁), α_1 , α_2	30-60	180-300
S/N-TCA	Doxepine		H ₁ , M ₁ , α_1	25-75	150-300
S/N-TCA	Imipramine		M ₁ , α_1	25-75	150-300
S/N-TCA	Dibenzepine			120-180	240-720
S/N-TCA	Dosulepine / Dothiepin			75	75-150
S/N-TCA	Protriptyline			10	20-60
N-TCA	Desipramine		(M ₁)	25-75	100-300
N-TCA	Lofepramine		M ₁ , α_1	70	140-210
N-TCA	Nortriptyline	SRI	M ₁ , α_1	25-50	75-300
S-TCA*	Setiptiline		α_1 , α_2	3	3-6
S-TCA*	Mianserin	(NRI)	H ₁ , α_1 , α_2	30	60-120
N-TCA*	Amoxapine			50	100-400
N-TCA*	Maprotiline		H ₁ , (M ₁), α_1	25-75	150-225

1 * tetracyclic antidepressants

Legend (primary modes of action are explained in the text)

+5-HT₁ = serotonin 1 receptor stimulation

5-HT₂ = serotonin 2 receptor antagonism

5-HT₃ = serotonin 3 receptor antagonism

5-HT_{1A} = 5-HT_{1A} receptor antagonism

5-HT_{2A} = 5-HT_{2A} receptor antagonism

all. 5HTT = binding to the allosteric site of the serotonin transporter

DA = dopamine receptor antagonist

DNRI = dopamine and noradrenaline reuptake inhibitor

DRI = dopamine reuptake inhibition

H1 = blockade of histamine 1 receptors

M₁ = blockade of cholinergic muscarinic receptors

MAOI = irreversible inhibitor of monoaminooxidase A and B

MAOBI = irreversible inhibitor of Monoaminooxidase B

MASSA = melatonergic MT₁ and MT₂ receptor agonist and selective serotonergic 5-HT_{2C} receptor antagonist

NARI = selective noradrenalin reuptake inhibitor

NaSSA = noradrenergic and selective serotonergic antidepressant

NRI = noradrenaline reuptake inhibition

N-TCA = tricyclic (or tetracyclic*) antidepressant with primary noradrenergic effects

RIMA = reversible inhibitor of monoaminooxidase A

SMA = serotonin modulating antidepressant

SNRI = selective serotonin and noradrenalin reuptake inhibitor

S/N-TCA = tricyclic (or tetracyclic*) antidepressant with similar serotonergic and noradrenergic effects

SRI = serotonin reuptake inhibition

SRS = serotonin reuptake stimulation

SSRI = selective serotonin reuptake inhibitor

S-TCA = tricyclic (or tetracyclic*) antidepressant with primary serotonergic effects

Despite the development of a variety of new antidepressants with different pharmacodynamic profiles, the hope of a better efficacy and clinical effectiveness in comparison to the first generation antidepressants has not been fulfilled up to now. Some positive reports of a better efficacy of some third generation antidepressants need further confirmation. In addition it is necessary to evaluate the clinical relevance of small mean differences in depression rating scales between active substances or antidepressant and placebo treatment, even in the case of statistical significance. Moreover also the results of failed trials, e.g. due to high placebo response rates, and the probably huge amount of still unpublished data of clinical trials should be evaluated before recommendations in favor of specific substances could be given. A further problem is the lacking information about both efficacy and tolerability of antidepressants in large sections of the world population. Predominantly genetic, but also cultural differences may contribute to a differential reaction of ethnic groups during antidepressant treatments. Especially a lack of information about the treatment effects of the

most and especially newer antidepressants e.g. in the black African population has to be taken into cautious consideration during the interpretation of the existing literature. Nevertheless the main advantage of second and third generation antidepressants is the overall better tolerability and safety in comparison to older substances. But although newer antidepressants are better tolerable and cause lesser side effects, their specific side effect profile has to be taken into account during antidepressant therapies. In addition the latency of several weeks until the onset of sufficient therapeutic effects remains a serious and clinically relevant problem. This principle holds true for each antidepressant and each class of antidepressant mechanisms. A faster onset of response has been described in some publications for newer dually acting compounds e.g. mirtazapine (Benkert et al., 2000; Leinonen et al., 1999; Montgomery, 1999) and venlafaxine (Benkert et al., 1996; Montgomery, 1999). The fact that after total or partial sleep deprivation a rapidly occurring antidepressant effect can be seen in two thirds of patients (Wu et al., 1990) (see chapter 15.3.5) shows in an impressive way that it is possible to achieve clear cut antidepressant effects within a very short time period. However, in most cases this effect is not persistent. At present, such a rapid improvement cannot be reached with any of the available antidepressant pharmacotherapies. The only therapeutic intervention which is more potent than sleep deprivation and leads to a more rapid improvement than pharmacotherapy as described in chapter 15.3.1 is ECT (ECT review group, 2003; Gangadhar et al., 1982). However, especially in case of patients who experienced antidepressant treatment failures, also ECT often needs several weeks until clinical improvement can be achieved. Furthermore, up to now ECT is an underrepresented therapeutic option in clinical routine, in spite of its proven efficacy.

A further general problem in pharmacotherapy of depression is the overall nonresponse rate of approximately 30% to the first antidepressant treatment (Charney et al., 2002). Besides clearly comprehensible biological hypotheses for therapy resistance like occult medical conditions

causing depression, substance abuse interfering with antidepressant treatments, or an abnormal metabolism (Rush et al., 2003b) it was also hypothesized that besides psychiatric comorbidities psychosocial factors could be responsible for failed treatment trials (Grote et al., 2003). Usually, a change of therapeutic strategies e.g. the prescription of another antidepressant of another mode of action or a combination therapy is recommended. Strategies to enhance therapeutic effectiveness such as lithium augmentation (Bauer et al., 2003; Zullino et al., 2001) or augmentation using thyroid hormones (Bauer et al., 1998) and other available methods are described in chapter 11.14. In addition the concomitant use of benzodiazepines e.g. lorazepam in agitated depression or alprazolam in anxious depression (Möller, 2002) can be a clinically useful addendum, the prescription of anxiolytics as a monotherapy is barely effective in severe depression (Laakmann et al., 1996). In case of further nonresponse, ECT is still the method of choice for treatment resistant depression (Davidson et al., 1978; ECT review group, 2003; Folkerts et al., 1997; Kroessler, 1985). ECT should only be administered after obtaining informed consent⁸ and in the so called "*modified form*" (which to date represents a standard procedure), i.e. with the use of anesthesia and muscle relaxation (WHO, 2005). The practice of using *unmodified* ECT should be stopped (WHO, 2005), but up to now this method still is in use in some countries in dependency of local habits and financial means. Of course per definition resistance to pharmacotherapy used as primary treatment implies that sufficient treatment attempts have been made with efficacious psychotherapies like cognitive-behavioral therapy (CBT) or interpersonal psychotherapy (IPT) (Thase et al., 1997). In the following available antidepressants are described according their mode of action, clinical effectiveness and predominant side-effect and risk profile.

⁸ Only in case of perilous diseases without the possibility to get the informed consent due to the character of the mental illness, ECT also can be administered after legal authorisation and informed consent of the patients' relatives.

11.2 Summary of side effects

The use of TCAs appeared to be problematic in some cases due to their inherent side effect profile. Particularly anticholinergic and antihistaminergic side effects caused considerable problems. A consequence was the development of new antidepressants with a more selective mode of action. But although newer antidepressants have considerably fewer anticholinergic effects, it is important to pay attention to the specific side effect profiles of the newer substances. In particular, the activating properties of noradrenaline reuptake inhibitors can cause tremor and restlessness together with sleep disturbances, serotonin reuptake inhibiting substances can result in nausea, headache, agitation, sexual dysfunction and sometimes sleeplessness. Substances with additional antihistaminergic properties such as mianserin, mirtazapine or doxepine especially during the beginning of the treatment may induce drowsiness, later often increased appetite weight gain emerges as a problem influencing compliance markedly (Kent, 2000). Especially during the first days of the use of antihistaminergic antidepressants patients have to be informed about a possible influence on their driving performance. But also an untreated depression usually worsens the patients driving performance due to prolonged reaction times and concentration deficits. After the first week of treatment (Ramaekers, 2003) and during long term treatment usually the driving ability normalizes. The normalization may be dependent of the applied daily dosages. In addition also differences in the driving performance between the treatment with sedating or nonsedating antidepressants have been reported (Ridout et al., 2003; Wingen et al., 2005). The specific side effect profiles in dependence on the receptor blocking and neurotransmitter influencing properties of antidepressants are summarized in Table 10. Using this table in combination with Table 9 the specific side effect profile which can be expected using a specific antidepressant can be seen.

Table 10

Modes of action and receptor profiles of antidepressants possibly associated with clinically relevant and compliance influencing side effects

Influenced receptors or neurotransmitters	Mode of action	Typical side effects
M₁ receptor	Antimuscarinic / Anticholinergic	<ul style="list-style-type: none"> • • Dry mouth • Accommodation disturbances • Constipation • Miction disturbances • Worsening of narrow angle glaucoma • Cognitive disturbances • Delirium • Cardiac arrhythmias
H₁ receptor	Antihistaminergic	<ul style="list-style-type: none"> • • Sedation • Drowsiness • Daytime tiredness • Increased appetite • Weight gain • Metabolic syndrome
α_{1/2} receptor	Antiadrenergic	<ul style="list-style-type: none"> • Hypotonia
NA transporter	Noradrenalin-Reuptake inhibition	<ul style="list-style-type: none"> • • Tremor • Tachycardia • Restlessness • Sleep disturbances • Hypertonia
5-HT transporter	Serotonin-Reuptake inhibition	<ul style="list-style-type: none"> • • Nausea • Decreased appetite • Weight reduction • Headache • Restlessness • Sleep disturbances • Sexual dysfunction • Serotonin syndrome • SIADH⁹ • Enhanced bleeding risk

11.2.1 Addiction to antidepressants

Addiction or dependence to some drugs – most notably alcohol and the opiates - represents a major health problem. DSM-IV defines ‘substance dependence’ in relation to a mixed picture

⁹ Syndrome if inadequate secretion of antidiuretic hormone, possibly resulting in hyponatremia and generalized epileptic convulsions

of tolerance, withdrawal effects and compulsive drug taking behavior, usually accompanied by craving for the positive effects of the drug. Haddad (Haddad, 1999) identified 21 English language case reports of antidepressant addiction (DSM-IV 'substance dependence' criteria) published since 1963. Sixteen involved tranylcypromine or amineptine, which have atypical dopaminergic and stimulant properties. Subject characteristics included male sex (14/21), personality problems (10/21) and prior substance misuse (14/21). The features of addiction such as tolerance and compulsive use are exceptionally rare with antidepressants, and antidepressants do not have a market value to drug misusers, an authentic measure of abuse potential. Addiction, in what is currently the accepted sense of the word is, accordingly, not clinically associated with most classes of antidepressant.

The belief that it is possible to become addicted to antidepressants is, nevertheless, widely held within society. It is promoted by anecdotal reports in which individuals claim to have had severe withdrawal symptoms and to have extreme difficulties in stopping taking antidepressants. It has also been painted into a broader image of conspiracy to intoxicate the public by lay authors such as Charles Medawer who puts his position as follows (<http://www.socialaudit.org.uk/60403162.htm>):

Both literally and metaphorically, all the drugs in this story cause some degree of dependence. People get hooked not only on the drugs, but also on the idea of drugs as solutions for mental distress. Subtle interplays of power and dependence nurture this process of medicalisation, as if through a 'Conspiracy of Goodwill'.

Addiction, on this basis, becomes equated with the side effects of drugs, and even ideas about drugs. It is, one must suppose, a matter of debate where it is reasonable to use the emotive term addictive and where it isn't. But DSM-IV, whatever its limitations, seems more accurately to capture the real hazards of addiction, and on the basis of that, antidepressants are not, as a class, substances of misuse and hence should not be described as addictive.

However, it would be surprising if psychotropic drugs did not produce some withdrawal effects on their discontinuation. Clearly they are often taken for relatively long periods of time and significant receptor adaptations take place to their presence. These changes, once the drug is removed, will be expressed as imbalances in neurotransmitter function and of subjective adverse effects. In a prospective survey of 97 patients stopping a SSRI (Bogetto et al., 2002), the onset of symptoms occurred within 2 days on average. Discernible effects were more likely with high doses and prolonged treatment. With less than five weeks exposure, withdrawal effects are very unusual and would be unexpected. When it occurs, a discontinuation syndrome is particularly dramatic in newborns, whose mother was treated with serotonergic drugs till delivery (Isbister et al., 2001; Misri et al., 2002; Nijhuis et al., 2001; Wen et al., 2006).

It is broadly correct that there are a range of abnormal experiences that can follow acute discontinuation and these tend to be most striking in drugs with relatively short half lives like paroxetine and venlafaxine (Rosenbaum et al., 1998). The symptom categories seen with SSRIs and venlafaxine are disequilibrium (giddiness or even vertigo), sensory abnormalities (e.g. headache), gastrointestinal upset (e.g. nausea), general somatic distress (e.g. lethargy), sleep disturbance and affective symptoms (Fava et al., 1997; Haddad, 1998). It should, of course, be a critical part of the information given to patients that such effects can arise. They can usually be abolished by re-starting the withdrawn drug and avoided by substituting fluoxetine to cover withdrawal, since it has a prolonged half-life.

In the war of words and their meanings that have invaded this debate, 'withdrawal' seems to be used synonymously with dependence and addiction by some authors and the term 'discontinuation' seems to be preferred by those who feel the effects are too mild to be regarded as evidence of a serious problem. The frequency and severity of withdrawal symptoms is a key issue. Withdrawal symptoms after long-term use of antidepressants are symptoms not related to the disease, but to drug tapering or stoppage. They have to be

distinguished from a recurrence of the actual depressive episode and from a rebound with symptoms of an even higher intensity (Bauer et al., 2002a). Unfortunately, the measurement of withdrawal effects is imprecise and will be confounded by expectations under ordinary clinical conditions. The more sensitive the measure the more likely it is that withdrawal effects are detected. It would however be extremely misleading to imply that these usually constitute a serious barrier to discontinuation in the majority of patients (Bogetto et al., 2002). When clinician and patient ratings are compared under double blind conditions, there is also a high level of agreement (Rosenbaum et al., 1998). This is important because the claim is sometimes made that companies and clinicians are in a conspiracy to deny how severe these symptoms are.

However, it would be surprising if there were not individual differences in the difficulties experienced on discontinuing a drug that can undoubtedly produce odd physical effects. About fifty comments on paroxetine withdrawal, from discussion boards posted between January 1999 and May 2002, were provided to the 'seroxat users' website (<http://www.seroxatusergroup.org.uk/>). There is a reasonable concordance with the symptoms described in the literature, in fact, although the effects are often described as very severe and unexpected. The apparent absence of appropriate information that such effects can occur runs consistently through the messages. There is also a pervasive hostility to the doctors (usually GPs it would appear) who prescribed the drug. It is a real challenge to know how to evaluate this evidence in a quantitative sense and also, qualitatively, in relation to the motivation and needs of people who use internet discussion boards. There is clearly a remarkable opportunity to harness patient experience through the internet, but a qualitative free-for-all is likely to be self perpetuating and ultimately uninformative because it is very likely to suffer from a variety of confounding biases. There is also the complication that there appears to be a prospect of secondary gain from suing multinational drug companies who own the patent on the

individual drugs. This issue is related to a much broader challenge, which is to improve current methods of post-marketing surveillance.

Finally, aside from the issues of addiction, but important from the point of view of management, it is certainly possible that on discontinuation patients may relapse with the original anxiety or depressive symptoms that promoted the use of antidepressants (Geddes et al., 2003). Clearly where this occurs, there is a clinical decision to be made between continuing with the medication and accepting the benefit of symptom control and discontinuing and seeing their return. There is no convincing evidence that the use of antidepressants makes returning anxiety or low grade depressive symptoms worse, but obviously the costs and benefits of long term use of any medication have to be weighed on an individual basis.

In conclusion, the consensus view among experts is that antidepressant drugs are not addictive in the normally understood sense of that word and as regularly applied for example to opiates. However, as with all medicines, their benefits come at the potential cost of adverse effects. Among these adverse effects include somatic symptoms on withdrawal. The extension of prescribing to minor symptoms or syndromes runs the risk of the harm being perceived to be greater than the benefit. There are undoubtedly some problems with the use and, particularly, the discontinuation of antidepressants that merit clinical care, clear labeling and information for patients and there seems little reason why, with that precaution, they should not be used safely. This is the usual experience of psychiatrists working in secondary care.

11.2.2 Use of antidepressants during pregnancy, postpartum depression and breast feeding

The pregnancy and postpartum periods are considered to be relatively high risk times for development of major depressive episodes in women (for review see (Cohen et al., 2004; Nonacs et al., 2003)). Both, acute and prophylactic treatment of MDD during pregnancy may be a difficult to solve therapeutic problem and requires an individual risk / benefit-analysis. In

addition during antidepressant pharmacotherapy after birth each available antidepressant is excreted in the milk and may influence infants during breast feeding (for review see (Burt et al., 2001; Suri et al., 1998)). Therefore the risk of an untreated MDD causing maternal stress influencing also the fetus and birth outcomes and an enhanced risk for suicide have to be evaluated together with an possibly enhanced risk for fetal malformations, growth impairment, fetal and neonatal toxicity and behavioral teratogenicity caused by antidepressant treatments (Wisner et al., 2000).

The benefits and risks of an antidepressant pharmacotherapy have to be evaluated and compared to other nonpharmacologic treatment alternatives, e.g. ECT (chapter 15.2) which can safely be administered during pregnancy and breast feeding (Rabheru, 2001; Walker et al., 1994), but also sleep deprivation (chapter 15.3.5) (Parry et al., 2000) or bright light therapy (chapter 15.3.7) (Oren et al., 2002) should be taken into consideration. Because no controlled studies about the use of antidepressants during pregnancy have been published, single case reports, case series and epidemiological data have to be reviewed carefully including the patients' individual history in the analysis. Not only the risk for malformations and neonatal complications have taken into account, but also to possible risk for an influenced behavioral development e.g. abnormal emotional behaviors in the offspring up to now cannot be excluded. Accordingly recent animal studies have shown an influence of serotonin and SSRI treatment on behavioral phenotypes which led to the hypothesis that these effects may indicate a critical role of serotonin in the maturation of brain systems that modulate emotional function (Ansorge et al., 2004).

The risk for intrauterine death or congenital malformations has primarily not been reported to be enhanced after treatment with TCAs and fluoxetine or other SSRIs (Wisner et al., 1999). Nevertheless more neonatal complications were seen. Children of mothers treated with fluoxetine during the first trimester of pregnancy showed lower maternal weight gain during pregnancy (which also can be seen during untreated MDD) together with a decreased birth

weight of the neonates and a higher rate of premature birth (Chambers et al., 1996). Moreover fluoxetine treatment of mothers during breast feeding caused a reduced growth of the infants (Chambers et al., 1999). The overall development of children of mothers receiving TCAs or SSRIs during pregnancy was not different in comparison to that of controls (Wisner et al., 1999). A meta-analysis reported that the use of newer antidepressants such as SSRI, SNRI, NARI, NaSSA and DNRI is not associated with an increased risk of major malformations above the baseline of 1-3% in the population (Einarson et al., 2005). Nevertheless a recent case-control study reported an association between the maternal use of SSRIs in late pregnancy and persistent pulmonary hypertension in newborns probably causing a substantially enhanced infant mortality (Chambers et al., 2006). In addition a warning not to use paroxetine within the first trimester of pregnancy has been published because of an twofold increase in the rate of cardiovascular malformations (GSK Clinical Trial Register; <http://ctr.gsk.co.uk/Summary/paroxetine/epip083.pdf>). Because less data and studies exist concerning newer antidepressants, it was recommended not to use compounds of which the information on teratogenic risks associated with exposure to these substances is incomplete or absent as first-line agents in the pharmacological treatment of depression during pregnancy and breastfeeding (Gentile, 2005). Even if reports about the safe administration e.g. of mirtazapine (Aichhorn et al., 2004) or escitalopram (Rampono et al., 2000) for mother and child during breast feeding have been published, their use of should be evaluated carefully. In addition also the specific safety profile of a maintenance and continuation therapies has to be considered during pregnancy and the post partum period (Ernst et al., 2002).

11.2.3 Precautions in case of disturbance of leucopoiesis

Not only neuroleptics such as clozapine or olanzapine (Duggal et al., 2004), but also mood stabilizer like carbamazepine (Sheehan et al., 1990) or lamotrigine (LeDrew et al., 2005; Ural et al., 2005) can cause or worsen neutropenia and thrombocytopenia. But also during

antidepressant monotherapy using a variety of substances including TCA (Gibson, 1974; Gravenor et al., 1986) or tetracyclic substances such as mianserin (Thomas et al., 1990) neutropenia is reported. Divergent reports about newer antidepressants such as SSRI (Ozcanli et al., 2005; Trescoli-Serrano et al., 1996), venlafaxine (Anghelescu et al., 2002; Lucht et al., 2000) and mirtazapine (NN, 2004; Ozcanli et al., 2005) are published. They have also been reported to have negative effects on leucopoiesis, but due to rare reports and frequent combination therapies the causal interdependencies are not clear. As a therapeutic or even prophylactic option additional Lithium therapy should be taken into account because of the potential not only to augment antidepressant therapies (Bauer et al., 2003) but also to stimulate leucopoiesis (Hager et al., 2002).

11.3 Selective serotonin reuptake inhibitors (SSRI)

11.3.1 Efficacy

Today SSRI are the antidepressant substances prescribed most frequent as a first line treatment. Good efficacy has been described for each of the currently available substances, regardless of etiology or severity of depression. Despite the publication of some statistical significant efficacy differences in some SSRIs, it is difficult to interpret the clinical meaning of these results (Cipriani et al., 2005). Also a statistically significant, but from a clinical point of view minimal superiority over other SSRIs (Moore et al., 2005) and a comparable efficacy to venlafaxine (Kennedy et al., 2006a) has been published for escitalopram. Prior meta-analyses showed neither significant nor clinical relevant differences in efficacy (Edwards et al., 1999). Nevertheless more RCTs should be awaited before the clinical relevance of these findings can be evaluated and final conclusions can be drawn and specific recommendations can be given.

In spite of the fact that SSRIs showed no overall relevant inferiority in comparison to TCAs in a variety of randomized controlled trials (Möller et al., 1998) and meta-analyses (Geddes et al., 2000), there is some evidence about better efficacy and clinical effectiveness of TCAs in the subgroup of in-patients in comparison to out-patients (Anderson, 1998; Anderson, 2000a). This was especially true, when the TCA amitriptyline was compared to SSRI. It has taken into account that in-patients show in most cases higher severity and a higher proportion of patients suffering from melancholic features of depression.

SSRIs and irreversible MAO inhibitors showed also a overall similar efficacy in the treatment of depression, only in outpatients suffering from depression with atypical features (chapter 5.2.1.4.3) a better efficacy of MAOIs could be shown (Thase et al., 1995). In addition MAOIs showed advantages during ultra-high-dose treatment in patients suffering from treatment resistant depression, whereas increasing the SSRIs dose showed no substantial beneficial effects (Adli et al., 2005).

11.3.2 Safety and tolerability¹⁰

The safety and tolerability profile of SSRIs in comparison to TCAs is considerably better (Mace et al., 2000). In detail especially anticholinergic side effects are more common during TCA therapy. Therefore a higher cardiovascular tolerability together with a lower risk for constipation and reduction of the urinary flow can be expected. Also anticholinergic side effects on the visual system such as an enhanced risk for worsening of a narrow angle glaucoma and accommodation disturbances are rare using SSRIs¹¹. The result are lower rates of discontinuations (Peretti et al., 2000) during SSRI treatment. In addition SSRIs are more safe in case of overdose in comparison to TCAs (Barbey et al., 1998; Cheeta et al., 2004; Mason et al., 2000), which provides more safety during antidepressant treatments especially

¹⁰ All possible interactions of antidepressants with other pharmacotherapeutics are beyond of scope of this review, the described interactions are a selection and not complete.

¹¹ Comment on paroxetine: in case of narrow angle glaucoma contraindicated due to more anticholinergic side effects in comparison to other SSRI

in cases of suicidality. In addition a simplified dose regimen in comparison to TCA therapy diminishes the danger of antidepressant therapies below therapeutic dose ranges. The mentioned factors contribute to an efficacious and cost-effective first-line therapy in depression in comparison to TCAs in spite of higher prescription costs (Goldstein et al., 1998).

Nevertheless clinicians have to be aware of the specific side effect profile of SSRIs (Ferguson, 2001; Lader, 1996). The most frequent side effects after short term treatment are gastrointestinal disturbances such as nausea, diarrhea or emesis. Also common are restlessness and agitation, sleep disturbances, dizziness, and headache. During long term SSRI treatment sexual dysfunction such as loss of libido, anorgasmia, and in men disturbances of erectile or ejaculatory function can be a limitation of SSRI therapy. These aspects seem to be less prominent during fluvoxamine therapy in comparison to other SSRIs (Waldinger et al., 1998). Paroxetine seems to be particularly responsible for delayed ejaculation (Montejo-Gonzalez et al., 1997). Disorientation, restlessness, myocloni together with hyperreflexia, tremor and pain-syndromes represent the so called serotonin syndrome. It can occur as an interaction of combining SSRIs with MAOIs or other serotonergic substances (e.g. S-TCAs or triptanes used during acute therapy of migraine attacks), even during time intervals before and after treatment in dependency of the half-life of the used substances. In most cases therefore a wash-out period of two weeks is recommended and SSRI / MAOI combination is contraindicated.

Rare side effects are weight gain, anticholinergic effects or extrapyramidal motor side effects (EPMS), especially in patients suffering from Parkinson's disease. After SSRI treatment even discontinuation symptoms may occur (Montgomery et al., 2004b) (for details see chapter 11.2.1). A very rare adverse event during SSRI therapy of younger, but a not uncommon event in elderly patients, is an inappropriate secretion of antidiuretic hormone (ADH) possibly causing an electrolyte imbalance and hyponatremia with an increased seizure risk (Arinzon et

al., 2002; Degner et al., 2004; Finfgeld, 2003). In addition the combined use of SSRIs and substances increasing the risk of bleeding events is discouraged due to blockade of serotonin reuptake in platelets and subsequent platelet dysfunction (Serebruany, 2006). Especially the risk for gastrointestinal hemorrhage seems to be enhanced if nonsteroidal antiphlogistics or aspirin are combined with SSRIs (Weinrieb et al., 2005). Discontinuation symptoms can occur after SSRI treatment (Haddad, 2001), but seem to be rare events after treatment with some newer SSRIs, e.g. sertraline (Sir et al., 2005) or escitalopram (Baldwin et al., 2005a).

11.4 Selective serotonin and noradrenaline reuptake inhibitors (SNRI)

11.4.1 Efficacy

SNRIs represent a group of newer, so called “second-generation” antidepressants acting dually on serotonin and norepinephrine reuptake. Today three substances of this group, venlafaxine, milnacipran and duloxetine, are available. Judging on the comparative efficacy and clinical effectiveness is difficult, because overall second-generation antidepressants probably do not differ substantially concerning these parameters for treatment of major depressive disorder (Hansen et al., 2005). Moreover a similar efficacy of the three SNRI has been suggested (Stahl et al., 2005), venlafaxine had shown only a trend to be favorable to reach remission, whereas response rates were comparable to that reached using duloxetine (Vis et al., 2005). In comparison to the SSRIs sertraline (Sir et al., 2005) and escitalopram (Bielski et al., 2005; Montgomery et al., 2004a) the SNRI venlafaxine demonstrated comparable effects concerning efficacy in treatment of major depression and quality of live whereas in a meta-analysis superior efficacy of venlafaxine over SSRIs has been shown (Smith et al., 2002), but due to the fact that most of the included studies investigated the efficacy of fluoxetine and paroxetine in comparison to SNRIs, these results have to be

evaluated carefully before conclusions about the efficacy of SSRIs as a pharmacological class can be drawn. The described superiority is reported to be enhanced, if not only response, but remission is used as an efficacy criterion (Stahl et al., 2005), but up to date no sufficient evidence for a faster response of SNRIs in comparison to SSRIs has been published. On the contrary direct comparisons between SNRIs (venlafaxine and milnacipran) and TCAs showed no significant or clinically relevant differences in efficacy (Samuelian et al., 1998; Van Amerongen et al., 2002).

11.4.2 Safety and tolerability

SNRI treatment showed a favorable tolerability profile in comparison to TCAs, the most adverse events are occurring early in treatment and have a tendency to decrease or disappear with continued treatment (Stahl et al., 2005). In comparison to the SSRI sertraline venlafaxine demonstrated comparable effects concerning efficacy in treatment of major depression and quality of life, but sertraline showed a more favorable tolerability profile concerning discontinuation symptoms and the risk of elevated blood pressure (Sir et al., 2005), which seems to be less prominent in newer SNRIs such as duloxetine and milnacipran (Stahl et al., 2005). Also after discontinuation of the SSRI escitalopram a lower rate of discontinuation emergent symptoms has been reported (Baldwin et al., 2005a). SNRIs in most studies showed a better efficacy in comparison to SSRIs and a better tolerability in comparison to TCAs, which at least in case of milnacipran probably has a positive impact on cost-effectiveness of the antidepressant treatment (Dardennes et al., 1999) (for more details on cost effectiveness of SNRIs see chapter 4.4.2). In case of overdose the fatal toxicity index of venlafaxine seems to be in between SSRIs and TCAs (Koski et al., 2005).

11.5 Selective noradrenaline reuptake inhibitors (NARI)

11.5.1 Efficacy

Controlled data directly comparing the single available NARI reboxetine to other antidepressants are rare. One study comparing reboxetine and sertraline found no difference in response after five weeks of treatment, whereas advantages of reboxetine between the second and fourth week and at week five in terms of remission were found (Eker et al., 2005). In comparison to fluoxetine an overall similar efficacy in MDD was found, but reboxetine was more effective in a subgroup of severely depressed patients (Massana et al., 1999). In comparison to citalopram in patients suffering from post-stroke depression a differential efficacy with greater efficacy of citalopram in anxious depressed patients and a better efficacy of reboxetine in retarded depressed patients was reported (Rampello et al., 2004). In addition it was summarized that reboxetine is at least as effective as other classes of antidepressants including TCAs and again in a subgroup of patients, in depressed patients with melancholic features an advantage in comparison to the TCA imipramine was found (Montgomery, 1998).

11.5.2 Safety and tolerability

In all published studies reboxetine showed a good safety and tolerability profile. Both safety and tolerability were improved in comparison to TCAs. NARI use was not associated with an increased risk of seizures, orthostatic hypotension or cardiovascular side effects. In addition sexual dysfunction appears less common with reboxetine than with the SSRI fluoxetine (Clayton et al., 2003). In comparison to SSRIs it has a different side effect profile and shows advantages in terms of agitation, nervousness, anxiety, and gastrointestinal events (Montgomery, 1998). Reboxetine treated patients sometimes experience agitation and sleep disturbances. In addition hyperhidrosis can disturb the patients. Despite the low

anticholinergic activity miction disturbances may occur. Also an increased heart rate and blood pressure have been reported. Weight loss rarely has been reported.

11.6 Monoaminoxidase inhibitors (MAOI, MAOBI, RIMA)

11.6.1 Efficacy

A comparable efficacy profile of all available irreversible MAOIs similar to that of TCAs has been reported, but this was only true in out-patients (Thase et al., 1995), even if they have been TCA treatment failures. In in-patients TCAs have been more effective than phenelzine and isocarboxazid. The responsivity to MAOI treatment was highest in patients suffering from depression with anergic or atypical features (Himmelhoch et al., 1991; Thase et al., 1992; Thase et al., 1995), but it has to be mentioned that anergic features were predominantly investigated in bipolar depression. In spite of this efficacy profile irreversible MAOIs are considered predominantly as a second-line treatment strategy because of their potential to cause serious adverse events (see below chapter 11.6.2) (Bauer et al., 2002b). Especially in depression resistant to TCAs treatment the use of MAOI monotherapy or the combination of MAOIs and TCAs or mood stabilizer has been suggested due to promising results of case reports and retrospective data analyses (Amsterdam et al., 2005; Feighner et al., 1985; Schmauss et al., 1988). Also dose escalating strategies with MAOI therapy were suggested, but only few clinical data show that tranylcypromine ultra-high-dose treatment may be effective in refractory depression (Adli et al., 2005). As described in chapter 5.2.6.2.3 also the MAO-B inhibitor selegiline which is predominantly used in the combination therapy of Parkinson's disease may exert significant, but sometimes only modest antidepressant effects (Amsterdam, 2003; Bodkin et al., 2002), but up to now only a selegiline transdermal system has been approved as an antidepressant by the FDA. The approval process in Europe still has not been finished. The reversible inhibitors of the Monoaminoxidase A (RIMA) have

considered to be as effective as TCAs and SSRIs but somewhat less effective than irreversible MAOIs (Lotufo-Neto et al., 1999). In case of moclobemide treatment higher dosages may enhance efficacy in severe depression (Lotufo-Neto et al., 1999).

11.6.2 Safety and tolerability

Due to possible interactions of predominantly irreversible MAOIs with sympathomimetic medication or tyramine containing food causing hypertensive crisis (Amsterdam et al., 2005; Brown et al., 1988) of potential fatal outcome, MAOIs are considered only as second-line antidepressants. Dietary restrictions preventing the ingestion of tyramine-rich food are necessary. MAOI ultra-high-dose therapy can cause delirium. In addition after irreversible MAOI therapy also withdrawal phenomena such as agitation, anxiety, sleeplessness or drowsiness and even hallucinations and delirium are described after discontinuing a MAOI therapy (Dilsaver, 1988). The risk for a serotonin syndrome due to the concomitant use or accidental combination of other serotonin enhancing antidepressants such as SSRIs, S-TCAs, SNRIs or SMAs has to be taken into account. In dependence of the half-life of the used substances a drug free time interval of at least 2 weeks in case of serotonergic medication before or after irreversible MAOIs is necessary to prevent severe adverse events. In case of the prescription of MAOIs after fluoxetine the time interval has to be lengthened up to 5 weeks, in case of prescribing serotonergic substances after the RIMA moclobemide, it can be shortened to 3 days. Dietary restrictions concerning tyramine-rich food are not as strict as using irreversible MAOI, however in dose ranges e.g. for moclobemide¹² above 900mg/d the risk of interactions with tyramine might become again clinically relevant (Bonnet, 2003). Moreover also RIMAs interact with concomitant used serotonin-enhancing drugs (Livingston

¹² During the licencing process from a clinical point of view too low doses have been recommended possibly due to marketing / pricing strategies. In the UK in comparison to other countries a 200% dose has been proposed, in Germany some month after introduction to the market the same recommendations have been given.

et al., 1996), causing severe serotonin syndromes (Dardennes et al., 1998; Guma et al., 1999; Roxanas et al., 1998).

11.7 α_2 -receptor blocking tetracyclic antidepressants

11.7.1 Efficacy

Up to date the structurally similar tetracyclic antidepressant mianserin and mirtazapine are representing the group of α_2 -receptor blocking antidepressants. Mirtazapine is characterized as an own class antidepressants with noradrenergic and specific serotonergic properties (NaSSA). The α_2 antagonistic effect in the case of mirtazapine is resulting in a serotonergic activation, whereas in case of mianserine the α_1 antagonistic effect is counteracting the α_2 antagonistic effect. Mianserin in addition exerts NA reuptake inhibiting effects. Both mianserin (Möller et al., 1995) and mirtazapine (Benkert et al., 2002) are described to be at least as effective as TCA and have some advantages in comparison to other second generation antidepressants (Szegeedi et al., 2005b). Especially in case of insomnia often accompanying depressive disorders mirtazapine significantly improves sleep parameters in addition to its antidepressant effects (Thase, 1999a). In comparison to SSRIs also a significant advantage in terms of a more rapid onset of action has been described (Benkert et al., 2000; Benkert et al., 2002; Blier, 2001; Blier, 2003; Quitkin et al., 2001; Tran et al., 2003), but due to the retrospective character of some of these studies, further clarification of the hypothesis, that these effects are not only caused by sedating properties of mirtazapine but also due to specific effects on other symptoms of depression, is warranted. In comparison to other so called third-generation antidepressants such as the also dually acting SNRIs and the selective NARI no convincing differences in terms of overall efficacy and speed of onset have been described (Möller, 2000; Olver et al., 2001). Nevertheless from a clinical point of view a significant advantage (and as later described in chapter 11.7.2 disadvantage at the same time)

of NaSSAs is their pharmacodynamic profile including antihistaminergic properties which are useful to treat depression related sleep disturbances without the use of additional hypnotic substances.

11.7.2 Safety and tolerability

In comparison to TCAs NaSSAs exert a side effect profile which is substantially improved in comparison to TCAs (Blier, 2003; Montgomery, 1995; Tran et al., 2003). Safety is similar to that of SSRIs (Olver et al., 2001), but typical serotonergic side effects such as sexual dysfunction and gastrointestinal complaints were less frequently present in mirtazapine-treated patients (Montgomery, 1995). The most frequently reported adverse events during mirtazapine therapy are antihistaminergic effects, such as initial somnolence and dizziness together with increased appetite and consecutive weight gain on the long term (Tran et al., 2003). Serious and potentially fatal side effects are rare, but clinicians have to be aware of the potential to cause or enhance neutropenia (Ozcanli et al., 2005) up to agranulocytosis, especially in patient population with an enhanced susceptibility (see chapter 11.2.3) and in combination therapies (Imbarlina et al., 2004).

11.8 Serotonin modulating antidepressants (SMA)

11.8.1 Efficacy

Nefazodone and its structural analog trazodone are blocking 5-HT₂ receptors and inhibit the reuptake of serotonin and noradrenalin. An equivalent efficacy in comparison to the TCA imipramine and other older antidepressants has been reported (Cyr et al., 1996; Ellingrod et al., 1995). In comparison to the SSRIs fluoxetine, sertraline and paroxetine also a similar effectiveness has been reported (Avila et al., 2003; Sussman et al., 2001). Trazodone was equally effective in comparison to the SNRI venlafaxine concerning the amelioration of

depressive symptoms, the amelioration of sleep disturbances was superior, but it showed less improvement in cognitive disturbances and retardation (Cunningham et al., 1994). In comparison to trazodone the NaSSA mirtazapine showed significant clinical advantages in terms of overall efficacy (van Moffaert et al., 1995). It was suggested that nefazodone and trazodone due to the sedating properties is in particular suitable for agitated patients and patients suffering from insomnia (Boerner et al., 1999; Thase, 1999a).

11.8.2 Safety and tolerability

In comparison to TCAs SMAs have a favorable tolerability profile (Lader, 1996) with a lower anticholinergic and antihistaminic activity (Taylor et al., 1995). The specificity of their action on the neurotransmitter systems is believed to be the cause for the enhanced safety and tolerability in comparison to TCAs (Nemeroff, 1994). The side effect profile is also different to that of SSRIs; the most common reported side effects are sedation, dry mouth, nausea, somnolence and dizziness (Cunningham et al., 1994; Cyr et al., 1996) and, in addition, in case of Trazodone the risk for priapism is enhanced. In comparison to SSRIs fewer complaints of nervousness, insomnia, and also sexual dysfunction were reported (Preskorn, 1995). Nevertheless during nefazodone treatment the potential for severe hepatotoxicity leading sometimes to a fulminant hepatic failure as published in several case reports (Conway et al., 2004; Schirren et al., 2000; Tzimas et al., 2003) is an important safety concern requiring reliable clinical monitoring (Lucena et al., 2003). Consequently the original producer has withdrawn nefazodone from the market, but in some countries including the USA it is still available as a generic substance.

11.9 Dopamine and noradrenaline reuptake inhibitors (DNRI)

11.9.1 Efficacy

In comparison to the SSRI sertraline (Coleman et al., 1999; Croft et al., 1999; Kavoussi et al., 1997), fluoxetine (Coleman et al., 2001; Feighner et al., 1991; Workman et al., 1993) and paroxetine (Weihs et al., 2000) bupropion showed a significant antidepressant efficacy of at least equal effect size. The same was true in comparison to the TCA doxepine (Feighner et al., 1986), but improvement of sleep parameters was more pronounced in the doxepine group. Also in comparison to the TCAs amitriptyline (Remick et al., 1982) and imipramine (Workman et al., 1993) no differences in efficacy could be seen. Within the same comparative study no efficacy differences in comparison to the SNRI venlafaxine and the SMA trazodone were found (Workman et al., 1993).

11.9.2 Safety and tolerability

In comparison to the SSRI sertraline bupropion treated patients showed a lower rate of serotonergic side effects such as sexual dysfunction, gastrointestinal complaints, insomnia and agitation (Coleman et al., 1999; Croft et al., 1999; Kavoussi et al., 1997). The same was true in comparison to fluoxetine treatment (Coleman et al., 2001). In comparison to TCAs predominantly more anticholinergic and antihistaminergic side effects were seen in patients receiving doxepine (Feighner et al., 1986). Even if the risk for generalized seizures is considered to be a rare consequence of bupropion treatment (Montgomery, 2005), this potential side effect has to be considered in treatment plans during bupropion use (Ross et al., 2005). At least in case of accidental or intentional overdose generalized seizures seem to be a relatively frequent complication (Pesola et al., 2002; Shepherd et al., 2004).

11.10 *Tri- and tetracyclic antidepressants (TCA)*

Since the introduction of the first antidepressant imipramine tricyclics have been the most important pharmacotherapeutic options in the treatment of depression during a long time period. The TCA amitriptyline even is mentioned within the WHO's list of essential drugs (World Health Organization, 2005b). Nevertheless during the last years tri- and tetracyclic antidepressants have lost their role as a first line treatment of depression in part due to their specific side effect profile and the introduction of second and third generation antidepressants. Even if there is not enough scientific evidence for this approach, from a clinical point of view to prepare antidepressant treatment plans it may be of use not only to subdivide TCAs according their sedating and activating properties, but also according their influence on serotonergic, noradrenergic and dopaminergic neurotransmission. Advances have been recently made in the knowledge about the pharmacological properties of tianeptine, a modified TCA stimulating serotonin uptake (Wilde et al., 1995). It has been hypothesized that neuroprotective effects (McEwen et al., 2005) may contribute to its known antidepressant properties (Defrance et al., 1988). Therefore alterations of neurogenesis and the neuroplasticity e.g. in the hippocampus may play also a prominent role for the efficacy of TCA, in case of tianeptine maybe even more than effects on serotonin reuptake. In case of treatment failures and pharmacotherapy resistance switching from serotonergic to noradrenergic or mixed acting TCAs seems to be plausible. But of course controlled studies supporting this approach still are lacking.

11.10.1 Efficacy

As described in the previous chapters TCA treatment is effective in MDD, independent of subtypes or severity of depression. Controlled studies comparing TCAs with other classes of antidepressants are provided within the chapters 11.3 up to 11.9. Especially in severe depressed hospitalized patients mixed S/N-TCAs seem to be of favor in comparison to SSRIs

(Anderson, 1998; Anderson, 2000a), whereas SSRIs and MAOIs seem to be superior in MDD with anergic or atypical features (Himmelhoch et al., 1991; Thase et al., 1992; Thase et al., 1995). From a clinical point of view, but without sufficient evidence in literature (Sartorius, 1974), TCAs with lesser sedating effects such as clomipramine or desipramine seem to be superior in retarded and anergic depression, TCAs with inherent stronger antihistaminergic effects such as doxepine, amitriptyline or dosulepine exert advantages in agitated patients with significant sleep disturbances.

11.10.2 Safety and tolerability

The main concerns in using TCAs as a first line treatment are anticholinergic and antihistaminergic side effects influencing tolerability and therapy adherence substantially. Sedating properties may be of use in the treatment of depression related sleep disturbances, but daytime drowsiness and sedation often lead to a discontinuation of the treatment. On the long term also the increased appetite, the consecutive weight gain and in some cases the risk even to enhance the high rate of metabolic syndromes in depression is playing a crucial role. Treatment safety can be enhanced by the use of more selectively acting modern antidepressants with a tolerability profile including a lower risk for cardiovascular or neurological side effects. In addition the modified TCA tianeptine does not appear to be associated with adverse cognitive, psychomotor, sleep, sexual dysfunction, cardiovascular or body weight effects. In addition suicide rates may be a further reason to be cautious in prescribing TCAs as first-line treatments; whereas SSRIs, NaSSA and SNRIs were associated with lower fatality of suicide attempts in case of drug overdose, a positive association between TCAs and fatal suicide attempts has been reported (Frey et al., 2002; Gibbons et al., 2005; Jonsson et al., 2004). The reason for this effect may be in spite of the efficacious treatment of depression using TCAs, an enhanced toxicity of these older substances in

comparison with the more selective newer antidepressants. This is especially true in case of overdose due to an enhanced cardiotoxicity.

11.11 Combination treatment

11.11.1 Combination of different antidepressants

11.11.1.1 Efficacy

Despite the fact that scientific evidence to define specific and effective next-step treatment options for treatment-resistant MDD still does not exist and is under current investigation (Rush et al., 2004) in case of nonresponse or partial response to antidepressant treatment combination of antidepressants is a very common strategy (de la Gandara et al., 2005a). In most cases antidepressants with different pharmacological profiles are combined. In a recent literature search, Dodd et al. (Dodd et al., 2005) identified only 8 randomized trials between 1978 and 2004 studying combinations of antidepressants, five of them including fluoxetine. In addition, 16 open label trials were identified, most of them using again at least one SSRI. Combining antidepressants with predominant serotonergic and noradrenergic properties, e.g. prescribing SSRIs and SNRIs is also clinically one of the most frequent therapeutic options (de la Gandara et al., 2005a). Also SSRIs and NaSSA in combination are used frequently. A combination of the SSRI fluoxetine and the tetracyclic α_2 -blocker (S-TCA) mianserin showed superior efficacy in comparison to placebo in several studies (Dam et al., 1998; Ferreri et al., 2001). Especially in case of prior treatment resistance also combining two dually acting substances such as mirtazapine and venlafaxine can be of clinical use, but more controlled studies confirming the superior effectiveness of such combinations are required (de la Gandara et al., 2005b; Rojo et al., 2005). Further reasons for combining different antidepressants are specific side effect profiles, e.g. using antihistaminergic properties of one antidepressant for early amelioration of sleep disturbances or improvement of appetite

especially in geriatric depression. Also lower rates of side effects. For example sexual dysfunction due to SSRI can possibly be improved using lower dosages within combination strategies, e.g. with bupropion.

11.11.1.2 Safety and tolerability

Combining two or even more antidepressants can enhance tolerability, due to clinical effectiveness of lower doses. At the same time due to a variety of possible pharmacokinetic interactions (Baumann, 1996) an enhanced risk for severe adverse events can be observed. This is especially true because therapeutic drug monitoring of these compounds is not widely used. A further enhanced risk may be present in case of additional somatic diseases requiring additional pharmacologic treatment.

11.11.2 Combination of ECT and antidepressants

11.11.2.1 Efficacy

ECT has been associated with rapid response and a higher percentage of response and remission in depressed patients in comparison to pharmacotherapy. Approximately 75-85% of depressed patients respond to effective ECT (Husain et al., 2004). But also lower response rates of 50-60%, especially in patients after repeated medication treatment failures, have been reported after the use of moderate dose unilateral ECT (Sackeim et al., 2000). In former publications using lower stimulation energy bilateral ECT has been shown to be more effective than unilateral ECT (Sackeim et al., 1987; Sackeim et al., 1993), but during the last years it was shown that unilateral ECT can be as effective as bilateral ECT if the dose regime allows to use a higher stimulation energy (Husain et al., 2004; Sackeim et al., 2000). But the increased efficacy is then accompanied by increased cognitive side effects, thereby marking that unilateral ECT has very limited advantages in that case (McCall et al., 2000). In certain cases subsequent clinical response can be achieved using bitemporal or bifrontal ECT or by

the administration of high-dose ECT. A further option to augment an ECT treatment course may be the concomitant prescription of antidepressants. However study results on a putative benefit combining ECT with TCAs (Lauritzen et al., 1996; Nelson et al., 1989) and the lack of advantages of other concomitant medication like SSRIs are still controversial (Lauritzen et al., 1996). Especially the efficacy of modern antidepressants in combination with ECT, e.g. the dually acting substances mirtazapine and venlafaxine, has never been investigated in controlled studies.

Due to the severity of depressive syndromes in patients after medication treatment failures, the clinical recommendation therefore is to combine ECT with antidepressants at moderate doses during the whole treatment course or at least during the last two weeks of ECT treatment to prevent exacerbation of depression after ECT during the usual latency until antidepressant response is achieved after initiating pharmacotherapy or to use continuation ECT (see chapter 15.2.3).

11.11.2.2 Safety and tolerability

The combination of ECT with TCA and SSRI has been described as a safe procedure (Lauritzen et al., 1996; Nelson et al., 1989). Also safety data about the combination of modern antidepressants with ECT are available: in a recent study venlafaxine at dosages lower than 300mg/day has been shown to be safe in combination with ECT. In high dose treatments above 300mg/d side effects of cardiovascular nature such as transient asystolia or bradycardia were more frequent if ECT was combined with propofol anesthesia (Lauritzen et al., 1996). The combination of ECT with MAOIs should be treated with caution and avoided if possible due to the enhanced risk for complications especially shortly after starting the pharmacological treatment (Naguib et al., 2002). A combination of ECT with lithium enhances anesthesia risks (Hill et al., 1976; Hill et al., 1977; Reimherr et al., 1977), the risks for prolonged seizures (Sartorius et al., 2005c) and the risk for cognitive disturbances, but

represents only a relative contraindication due to reports of a safe use of this combination and the specific risks discontinuing the lithium treatment.

11.12 *Herbal antidepressants*

11.12.1 Efficacy

It is a matter of ongoing controversy whether herbal antidepressants should be classified as antidepressants (Bauer et al., 2002b) , although they make up a reasonable share of antidepressant prescriptions in several countries, e.g., Germany. The main reason is that it has not been shown in RCTs that these medications are useful in severe depressive conditions; other reasons are their unknown precise pharmacological mechanism of antidepressant effects. Nevertheless, a variety of herbal substances with possible antidepressant effects have been investigated in less sophisticated studies and/or less severely depressed patients. For most of them, e.g. cava-cava extract, no antidepressant effects could be demonstrated. The most extensive investigations exist about the use of St. Johns wort (*hypericum perforatum*). It has to be mentioned that many different preparations of St. Johns wort are available in over-the-counter packages and that these differ in the numbers, concentrations and balance of active and inactive, helpful and potentially harmful constituents. Both, serotonergic mechanisms and MAO inhibition as antidepressant modes of action have been discussed (Deltito et al., 1998). In addition mechanisms similar to SSRIs in a smaller extent have been reported (Kasper et al., 1999). Despite some controversy in study results (Shelton et al., 2001a), it was concluded that *hypericum* is suitable for the treatment of mild to moderate depressive syndromes (Kalb et al., 2001; Kasper, 2001; Lecrubier et al., 2002; Uebelhack et al., 2004; Wong et al., 1998) if preparations provide sufficient concentrations of hypericin. In some countries it already has been approved for that indication. In randomized controlled studies *hypericum* was therapeutically equivalent to the SSRI fluoxetine (Behnke et al., 2002; Schrader, 2000),

paroxetine (Szegedi et al., 2005a) and sertraline (Brenner et al., 2000; Gastpar et al., 2005). Indirect comparisons with fluoxetine showed no relevant efficacy differences (Volz et al., 2000). Even advantages of hypericum in comparison to fluoxetine (Fava et al., 2005a), but without statistically significant superiority of both active compounds over placebo, have been shown. Nevertheless remission rates were higher in SSRI treated patients (Bjerkstedt et al., 2005). Therapeutic equivalence to imipramine and superiority over placebo have been shown in the treatment of mild to moderate depression (Philipp et al., 1999; Woelk, 2000). Recent metaanalyses show inconsistent results (Linde et al., 2005). It was stated that hypericum shows similar effectiveness as low-dose TCA (Kim et al., 1999) or SSRI therapy (Kasper et al., 2002) but design problems of some studies do not allow definite conclusions.

11.12.2 Safety and tolerability

Comparative studies showed a significant better tolerability in comparison to SSRIs and TCAs (Bjerkstedt et al., 2005; Szegedi et al., 2005a; Woelk, 2000). In peculiar hypericum therapy was devoid of anticholinergic side effects, sedation, gastrointestinal disturbances and sexual dysfunction (Trautmann-Sponsel et al., 2004). It has been considered to be safer in comparison to TCA with regard to cardiac function (Czekalla et al., 1997). Nevertheless risks to be aware of are photosensitization (Kasper et al., 1999; Kasper, 2001). Because hypericum involves serotonergic mechanisms or monoamine-oxidase inhibition, concurrent use of SSRIs and MAOIs should be avoided (Deltito et al., 1998). A treatment with hypericum, an inducer of both CYP_{3A4} and of the drug transporter protein P-glycoprotein can result in pharmacokinetic interaction with serious clinical consequences such as the loss of activity of the comedication (Henderson et al., 2002; Hennessy et al., 2002; Izzo et al., 2001), as shown for digoxine (Johne et al., 1999), cyclosporine (Ruschitzka et al., 2000) due to an induction of hepatic metabolizing enzymes, or contraceptives especially in case of low-dose oral contraception (Murphy et al., 2005).

11.13 *Ω-3 polyunsaturated fatty acids*

11.13.1 Efficacy

After the publication of a potential epidemiological link between low fish intake and depression (Hibbeln, 1998), low Ω -3 fatty acid levels in depression and in women during the perinatal period have been found (Rees et al., 2005). In four of seven double-blind randomized controlled trials a significant improvement of depressive symptoms could be seen after regular ingestion of eicosapentaenoic acid, an Ω -3 fatty acid as an adjunct to antidepressant treatment in comparison to placebo (Nemets et al., 2002; Peet et al., 2002) (for detailed information see the review of (Sontrop et al., 2006)).

Due to also published negative results (Silvers et al., 2005) up to now it remains unclear whether this therapeutic option has clear antidepressant effects. Furthermore it remains unknown, whether it could be effective independently of other antidepressant treatments or efficacious only in patients with abnormally low Ω -3 fatty acid levels.

11.13.2 Safety and tolerability

The safety and tolerability profile of Ω -3 fatty acid therapies seems to be excellent so far. A good tolerability even in postpartum depression has been reported (Freeman et al., 2006). Diarrhea is a very common side effect without markedly enhanced dangers for the treated patients, but it is able to influence blinding procedures in double-blind studies. Even a somatic benefit for depressed patients often experiencing enhanced cardiovascular risks has been proposed and should be investigated in further studies (Frasure-Smith et al., 2004).

11.14 *Augmentation strategies*

11.14.1 The concept of non-response to antidepressant treatment

Patients not responding to at least two antidepressant monotherapies (in some wider definitions even one) are usually defined as treatment resistant. However, reasons for such “treatment resistance” may vary and often do not reflect true resistance to treatment. The definition by Ananth (Ananth, 1998) as a “failure to respond adequately to two successive courses of monotherapy with pharmacologically different antidepressants given in adequate dose for sufficient length of time” includes a number of prerequisites: correct diagnosis, adequate treatment in terms of dosage, duration and compliance and unsuccessful previous therapy.

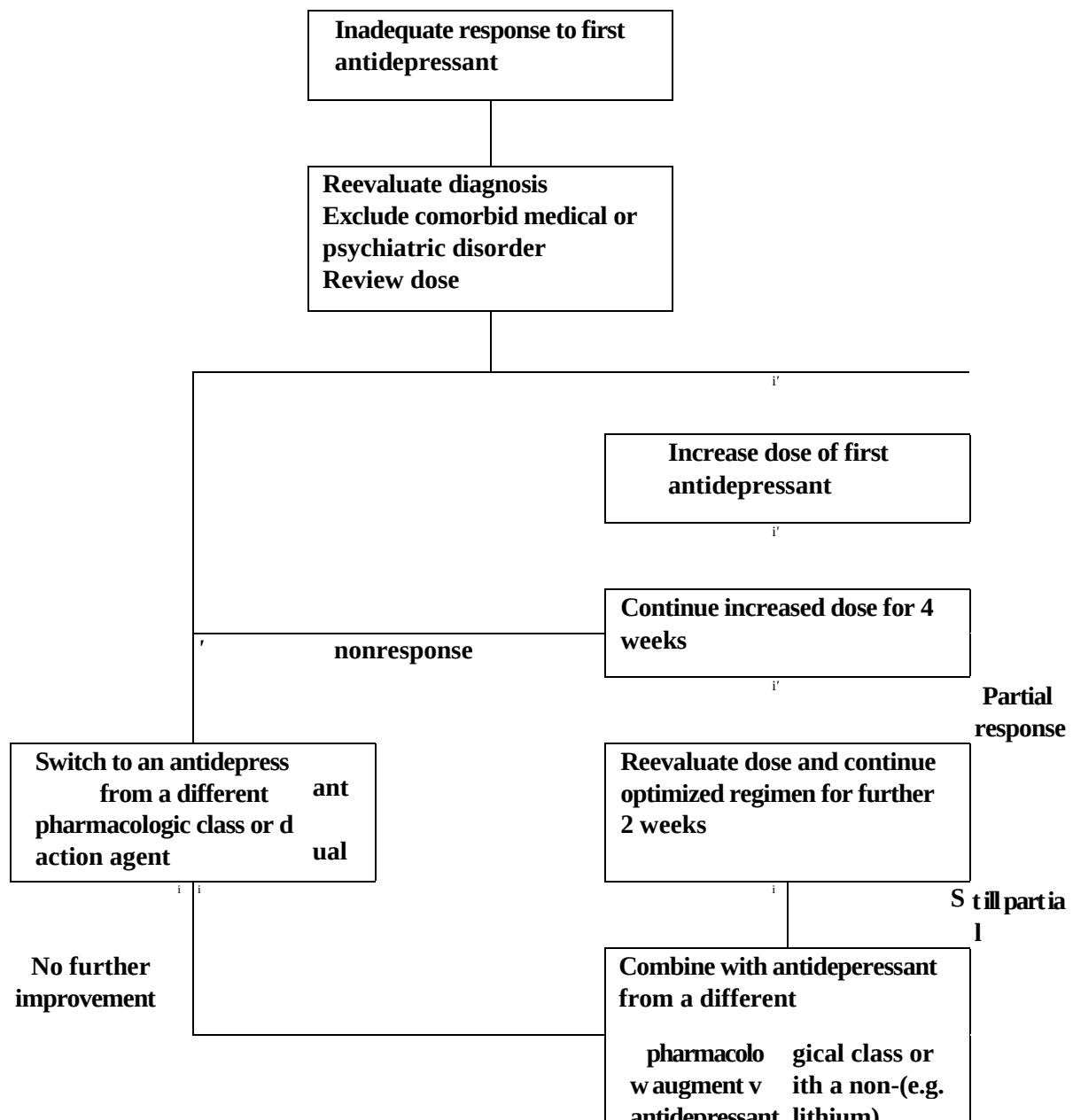
Before switching antidepressants, sufficient length of treatment (see chapter on “Acute treatment”) and the adequacy of dosage should be considered. If in doubt, TDM may be helpful to ensure adequate blood levels of medication (Corruble et al., 2000). Adli et al. (Adli et al., 2005) conducted a systematic review whether dose escalation may lead to additional benefit after a medium-dose treatment failed. They concluded that “Available data suggest differential efficacy of various pharmacological classes at more than medium-dosage. Direct evidence shows no increase of efficacy with high-dose selective serotonin reuptake inhibitor (SSRI) treatment; however, indirect evidence suggests enhanced therapeutic efficacy with high-dose tricyclic antidepressants. Few clinical data show ultra-high-dose treatment with the irreversible monoamine-oxidase-(MAO-) inhibitor tranylcypromine to be effective for refractory depression. Data concerning other selective compounds are insufficient to allow any definitive conclusion on the benefit of high-dose treatment.”

Factors besides pharmacological treatment resistance which may also lead to less favorable outcomes may include psychiatric comorbidity including alcohol- and substance abuse, personality disorders and anxiety- and panic disorder (Adli et al., 2005). Sharan and Saxena

have also identified several other factors predictive of poor response including a family history of affective disorders, severity of depression, suicide attempts, number of previous episodes, long duration of depression prior to treatment, negative life events and poor social support. Thus, awareness of these factors and adequate action, e.g. addition of psychotherapy with negative life events, are a priori requisite before pharmacological changes are made. Treatment resistant depression may also have an impact on the vulnerability to other mental disorders, e.g. the incidence of dementia is significantly increased in older patients with insufficiently treated depression (Shim et al., 2006). Supportive for this are also MR findings showing decreased hippocampal volumes in treatment refractory depressed patients, and enhancing neuronal plasticity and cellular resilience may be a new direction to develop novel, improved therapeutics for difficult-to-treat depression (Manji et al., 2003). Figure 3 summarizes a step-wise approach how to manage non-responsiveness to the first antidepressant.

Figure 3

A step-wise approach to management of the patient with inadequate response to antidepressant therapy (adopted from (Hirschfeld et al., 2002))



* Therapeutic drug monitoring (TDM) should be implemented in routine care (Mann et al., 2006b), it is especially recommended in case of treatment failures.

11.14.2 Combination and augmentation

In case that the previous monotherapy was not efficacious at all, even after a trial with a maximum dosage, switching of medication is usually recommended (Kennedy et al., 2001). A recently published analysis of the Star*D trial pointed out that approximately 25 % of patients non-responsive to citalopram have a profit from switching either to sertraline, bupropione and venlafaxine (Rush et al., 2006).

However, with a partial response it may often be unwise to discontinue the pre-medication and risk worsening of symptoms. Thus, combination with another antidepressant or augmentation should be considered, and there is now sufficient evidence that combination of antidepressants or augmentation strategies could be more effective than monotherapy in some patients (Kennedy et al., 2001). Combination treatment is defined as the addition of another medication without expecting potentiation of efficacy of the previous drug. Benefits as well as side effects are additive. Usually, a medication with an alternative and different pharmacology or a drug with a dual mechanism of action is chosen for combination treatment. In contrast, augmentation means the addition of another agent which by it self may be not specifically helpful as a primary treatment of depression, but may enhance responsiveness to a given antidepressant. Examples for these strategies, usually used in antidepressant non- or only partially responsive patients, include lithium, thyroid hormones, pindolol and buspirone and, more recently, also some atypical antipsychotics. Table 11 summarizes common augmentation strategies.

Table 11

Biological treatment strategies for partial and nonresponding patients with major depressive disorders. Modified from: WFSBP Guidelines for Biological Treatment of Unipolar Depressive disorders, Part 1 (Bauer et al., 2002b)

Treatment Strategy	Mechanisms / Drug Classification
Pharmacological Augmentation	
Lithium	Mood Stabilizer
Valproate, carbamazepine	Anticonvulsants/Mood stabilizer
Pindolol	5-HT _{1A} autoreceptor antagonist, β -receptor blocker 5-HT _{1A}
Buspirone	and D ₂ receptor agonist
Stimulants	Dopamine and noradrenaline release and reuptake inhibition
Bromocriptine	Dopamine (D ₂) agonist
Pergolide	Dopamine (D ₁ /D ₂) agonist
Reserpine	Reuptake inhibition of biogenic amines
Olanzapine, risperidone, aripiprazole	Antipsychotic agents, 5-HT ₂ antagonism
Hormone Augmentation	
Triiodothyronine (T ₃)	Thyroid hormone
L-Thyroxine (T ₄)	Thyroid hormone
Estrogen (only women)	Ovarian steroid hormone
Dehydroepiandrosterone (DHEA)	Adrenal androgen hormone
Miscellaneous	
Ketokonazole, metyrapone	Peripheral cortisol suppression
L-Tryptophan	Essential amino acid, 5-HT' precursor
Non-Pharmacological	
Electroconvulsive therapy (ECT)	Electric stimulation to elicit an epileptiform seizure in brain
[Repetitive transcranial magnetic stimulation (rTMS)]	Noninvasive stimulation of the cerebral cortex
[Vagus Nerve Stimulation (VNS)]	Autonomic signals to limbic and cortical function

Compared to switching antidepressants augmentation strategies have some advantages. They eliminate the period of transmission from one antidepressant to another and build on the

partial response. Consequently, if they work, they can be rapidly effective, however, they may also raise tolerability and safety issues.

As combination treatment has been dealt with extensively in the previous chapter (see chapter 11.11) we will now only concentrate on the different augmentation as strategies tested in unipolar depression.

11.14.2.1 Lithium

Of all strategies listed in Table 11 lithium augmentation has the best scientific evidence (Bauer et al., 2003; Zullino et al., 2001).

A multitude of open and 12 randomized, placebo-controlled trials including a metaanalysis (Bauer et al., 2003) support the efficacy of lithium augmentation in the acute treatment of treatment-resistant unipolar major depression. Lithium has been found to augment the therapeutic effects of a broad spectrum of antidepressants including TCAs (Bauer et al., 1999; Bauer et al., 2003) and SSRIs (Joffe et al., 1993; Katona et al., 1995). The meta-analysis by Bauer and Döpfner (Bauer et al., 1999) also demonstrated that lithium augmentation is superior to placebo augmentation, with a response rate of about 40 –50% at week 3 or 4 across studies, but only 20% of patients having an onset of response as early as week one. To allow full assessment of patients responsiveness, lithium augmentation should be administered for at least four weeks, ensuring serum levels of 0.6 – 0.8 mmol/L (Bauer et al., 2002b). However, the utility of lithium augmentation may be limited by side effects, e.g. polyuria, muscular weakness or tremor. Whether the potential neurotoxicity of Lithium plays a major role in clinical practice or even a distinct neuroprotective effect cannot be decided yet. This issue will be discussed in an extensive review to be published soon (Fountoulakis et al., 2006). It is also unclear whether lithium augmentation has the same efficacy across age groups. There are some publications pointing to a low response rate and a high rate of severe side-effects in the elderly. Lithium toxicity can occur even with therapeutic plasma levels and

might present itself with a clinical picture which is not always easy to differentiate from an increase in depression severity. EEG is an important tool for differential diagnosis in this clinical situation (Gallinat et al., 2000).

In addition, due to a relative neglect of lithium especially in North American guidelines over the last decades, many younger doctors are not so familiar with lithium and may thus refrain from its use.

11.14.2.2 Thyroid hormones

At least 13 prospective trials (nine open and four controlled double-blind studies) have supported the usefulness of triiodothyronine (T3), with most studies employing 25 – 35.5 µg/day (Bauer et al., 2002b). A three-arm, double-blind controlled study showed equal efficacy of augmentation with T3 and lithium and superiority to placebo (Joffe et al., 1993). However, as not all controlled double-blind studies yielded significant results in favor of T3, a subsequent meta-analysis found inconsistent results favoring T3 augmentation (Aronson et al., 1996). Recently, augmentation with L-Thyroxine (T4) has been postulated as an alternative to T3, and open studies and functional neuroimaging support the efficacy of this approach (Aronson et al., 1996; Joffe et al., 1993), however, double-blind controlled studies are still missing. When adding T4 evidence so far suggests that supraphysiological dosages should be used; comparison of only 150 µg/day T4 with 37.5 µg/day T3 showed significant lower response rates for T4 (24 vs. 53 %) (Svestka et al., 1990). In some studies, dosage up to 500 µg/day of T4 have been used showing good efficacy and satisfying tolerability (Svestka et al., 1990). However, the use of T4 in treatment resistant unipolar depression is still experimental, and more evidence still exists for T3.

11.14.2.3 Anticonvulsants

Surprisingly little evidence has been published so far about a potential augmentative effect of anticonvulsants in unipolar depression. For valproate (Davis et al., 1996; Svestka et al., 1990)

and carbamazepine (Post et al., 1986) open studies suggest antidepressant properties (Normann et al., 2002; Post et al., 1986). However, verification by double-blind studies is still missing and, in addition, studies on augmentation with carbamazepine showed that it induces metabolism of venlafaxine and citalopram, and therefore, it may be necessary to adapt the dose of the antidepressant (Ciusani et al., 2004; Steinacher et al., 2002). For lamotrigine, a double-blind add-on study to paroxetine in non-treatment resistant patients showed a faster onset of response, but no significant difference in the outcome after ten weeks (Normann et al., 2002).

As far as treatment resistant depression (TRD) is concerned, however, there is some evidence for augmentative efficacy of carbamazepine from open studies (Cullen et al., 1991; Rybakowski et al., 1999; Varney et al., 1993). For lamotrigine, augmentative efficacy has been reported both in open or retrospective studies (Barbee et al., 2002), but also in one small double-blind study (Barbosa et al., 2003); however, most of these studies (Barbosa et al., 2003; Blier et al., 2003) were conducted in mixed samples of unipolar and bipolar II patients without separate analysis, thus, they do not allow a clear conclusion as far as unipolar TRD is concerned. In summary, the evidence for the usefulness of augmentation with anticonvulsants remains weak.

11.14.2.4 Pindolol

A potential role of 5HT_{1A} agonists in treating depression and anxiety has been a major focus of research in the past decade (Blier et al., 2003). Pindolol is a β -adrenoreceptor antagonist. It also blocks 5HT_{1A} and 5HT_{1B/1D} receptors and therefore should prevent the negative feedback effect of increased somatodendritic serotonin (Dawson et al., 2000). As a consequence, this may accelerate the onset of antidepressant action (Artigas et al., 2001; Artigas et al., 2006).

A metaanalysis by Ballesteros and Callado (Ballesteros et al., 2004) of nine randomized controlled studies on the augmentative effects of pindolol to SSRI showed an increased responsiveness with pindolol after 2 weeks. However, after six weeks no difference in outcome was observed. Despite positive open studies, three out of four controlled trials have failed to show advantage over placebo in treatment refractory patients (Moreno et al., 1997; Perez et al., 1999; Segrave et al., 2005); only one small study applying once-daily high dose pindolol (7.5 mg) demonstrated a significant advantage (Sokolski et al., 2004). In their review on pindolol augmentation, Segrave and Nathan (Segrave et al., 2005) speculate that the 2.5 mg t.i.d. dose of pindolol that has been used in all but one of these investigations may be suboptimal for achieving reliable and significant occupancy of 5-HT_{1A} autoreceptors, as shown by PET data (Rabiner et al., 2001) and may explain the contradictory nature of the results of investigations of pindolol augmentation.

11.14.2.5 *Buspirone*

Buspirone is a partial 5-HT_{1A} antagonist that is believed to activate postsynaptic 5-HT_{1A} receptors and thus may enhance the action of SSRI. In addition, a major metabolite of buspirone enhances norepinephrine release. Therefore, buspirone may also exert a dual mechanism of action. However, in two double-blind placebo-controlled studies, buspirone augmentation either to fluoxetine or citalopram failed to demonstrate significant benefit over placebo (Appelberg et al., 2001; Landen et al., 1998). The study by Appelberg, however, suggested at least a potential benefit in more severe depression in a post-hoc sub-analysis (Appelberg et al., 2001). Recently, the STAR*D study investigated the efficacy of buspirone vs bupropion augmentation in SSRI non responders. In most outcomes, the rate of improvement was similar for both strategies, however, buspirone was associated with more tolerability problems (Trivedi et al., 2006). Clearly, further controlled studies are required to clarify the role of 5-HT_{1A} agonist in augmenting antidepressants.

11.14.2.6 *Atypical antipsychotics*

More recently, the use of atypical antipsychotics to augment antidepressants also in non-psychotic major depression has been advocated. In rat prefrontal cortex, Zhang et al. could demonstrate that the combination of olanzapine and fluoxetine produced robust, sustained increases of extracellular levels of dopamine and norepinephrine up to $361 \pm 28\%$ and $272 \pm 16\%$ of the baseline, respectively, which were significantly greater than either drug alone (Zhang et al., 2000). Thus, the combination of olanzapine and fluoxetine has been tested in several controlled studies both in unipolar, and, more extensively, bipolar depression. A small placebo-controlled study of olanzapine add-on to fluoxetine supports this strategy (Shelton et al., 2001b). More recently, a larger double-blind study comparing monotherapy with fluoxetine, nortriptyline and olanzapine against olanzapine/fluoxetine combination in TRD patients was also significantly in favor of antidepressant/antipsychotic combination (Shelton et al., 2005). In addition, a large open study showed acute responsiveness of previously SSRI (citalopram) treatment resistant patients to augmentation with low doses (0.25-2mg/d, depending on age) risperidone (Nemeroff et al., 2004). After a 6-week augmentation phase, 68.1 % of the TRD patients receiving add-on risperidone were classified as responders. However, significant superiority against citalopram monotherapy was not maintained in the subsequent double-blind continuation phase.

Recently, another placebo-controlled study on risperidone augmentation in TRD patients has been presented including 97 patients who met criteria for unipolar nonpsychotic major depression and failed to respond, or only partially responded, to at least a five week trial of an adequate dose of antidepressant monotherapy. Primary outcome (remission status) was determined by a Montgomery-Asberg Depression Rating Scale (MADRS) rating ≤ 10 to denote remission. At the end of four weeks of treatment 51.6% of the risperidone augmentation group remitted compared to 24.2% of the placebo augmentation group ($p=.011$) (Nemeroff et al., 2004).

Augmentation with risperidone has also been compared to addition of Bupropion as a second antidepressant to SSRI in a small, double-blind study. Although there was no significant difference in any outcome score at study end (week 6), risperidone produced a more robust effect as early as week 1 (Papakostas et al., 2004).

For ziprasidone (Papakostas et al., 2004) and aripiprazole (Barbee et al., 2004; Papakostas et al., 2005; Papakostas, 2005; Simon et al., 2005), first open and retrospective data also support augmentative efficacy, however, controlled studies are not yet published.

In conclusion, augmentative effects of several atypical antipsychotics have been described, however, controlled evidence is still sparse, comparator studies to established strategies as lithium augmentation are lacking and we still need more clinical experience of their utility in treatment resistant depression.

11.14.2.7 Other augmentation strategies

L-tryptophan and 5-hydroxytryptophan as serotonin precursors have been studied in depressive disorders with equivocal results. Some smaller studies using L-tryptophan showed potentiation of MAOIs and augmentation of serotonergic antidepressants in TRD (for an overview: see (Nelson, 2000)) and in seasonal depression refractory to light treatment (Lam et al., 1997). However, unambiguous controlled studies are still lacking. Since an open pilot trial by Wharton with methylphenidate in TRD (Wharton et al., 1971), the use of stimulants has been documented in case series and one larger retrospective chart review suggesting efficacy in treatment refractory depression (Stotz et al., 1999). However, the so far only randomized controlled study with methylphenidate in TRD (Zhang et al., 2000) could not find a significant advantage over placebo.

More recently, modafinil has been tested in an open pilot studies as an add-on to antidepressants showing a 43 % response rate (Rasmussen et al., 2005). In a placebo-controlled study, however, it showed significant improvement in SSRI partial responders for

fatigue and sleepiness, but only a trend to better outcomes in depression rating scales (Fava et al., 2005b). Clearly, more randomized, confirmative studies are needed. Besides acting against agitation and sleep disturbances, antidepressants may also have other augmentative effects on antidepressant treatment (Furukawa et al., 2000; Furukawa et al., 2001). However, their long term use is clearly discouraged due to their inherited risk of addiction.

In some instances, e.g. perimenopausal depression, augmentation with estrogen has been recommended based on small pilot studies (Morgan et al., 2005; Rasgon et al., 2002; Schneider et al., 1997; Schneider et al., 2001). However, the use of estrogen has inherited health risks as increased risk of endometrial and breast cancer and thrombosis. A recent randomized, double-blind pilot study tested antidepressant augmentation with the selective estrogen receptor modulator raloxifene, showing good tolerability of raloxifene and a nonsignificant trend to higher remission rates after 8 weeks (Grigoriadis et al., 2005). Clearly, more controlled studies with adequate sample sizes are demanded.

11.14.2.8 Summary

In summary, except of lithium and T₃ there is still a lack of good methodological studies supporting other pharmacological augmentation strategies. Recently, this area received more scientific attention and ongoing studies like the Sequenced Treatment Alternatives to Relieve Depression (Star*D) study of the NIMH (Fava et al., 2003; Trivedi et al., 2004), the Texas Medication Algorithm Project (Rush et al., 2003a; Trivedi et al., 2004) or the Berliner Algorithmus Projekt (Adli et al., 2002; Adli et al., 2003) will supply further evidence for augmentation strategies in the near future and develop evidence based algorithms for treatment refractory patients.

11.15 New developments and novel pharmacological treatment approaches

The therapeutic latency, the non-response rate of approximately 30% and the side effects of all antidepressants available so far are important reasons to continue the search for further treatment options for depressive disorders. During the following chapters some of the new pharmacological principles that may disclose novel approaches in the treatment of depression are described (Baghai et al., 2006; Rupprecht et al., 2004).

11.15.1 Influence on melatonergic neurotransmission

Melatonin secretion underlies strict circadian rhythms (Lesieur et al., 1998). It is regulated via the cAMP signal transduction cascade (Foulkes et al., 1997). A variety of animal studies and clinical trials in depressed patients suggest that agomelatine, a synthetic melatonergic MT₁ and MT₂ receptor agonist (Millan et al., 2003) with serotonin (5-HT)_{2C} receptor antagonist (Millan et al., 2003) properties within the central nervous system (CNS), has antidepressant effects (Tuma et al., 2002). Agomelatine therefore may represent a new class of melatonin agonistic and selective serotonin antagonistic antidepressants (MASSA). The antidepressant properties and a good tolerability profile of agomelatine have been demonstrated in several clinical trials (Kennedy et al., 2006b; Loo et al., 2002; Montgomery et al., 2004b; Olie et al., 2005) in comparison to the established antidepressants such as paroxetine and venlafaxine and to placebo. In addition especially sleep-related complaints were ameliorated without sedation during the daytime. In a further randomized, double-blind, multicenter study the absence of discontinuation symptoms in sustained remitted patients after agomelatine therapy could be shown (Montgomery et al., 2004b). In summary agomelatine represents a promising novel strategy in the treatment of depression.

11.15.2 Serotonergic antidepressants

Gepirone is an azapirone, similar to buspirone, which acts as a partial agonist at 5-HT_{1A} receptors (Silva et al., 2000; Van Reeth et al., 1999). In animal studies gepirone shows anxiolytic and antidepressant properties (Silva et al., 2000; Van Reeth et al., 1999). Up to now three placebo controlled double-blind studies in depressed patients have been published. In all trials gepirone was superior to placebo in the treatment of depression, in addition a good tolerability has been shown (Feiger, 1996; Feiger et al., 2003; Wilcox et al., 1996). Although these data support possible antidepressant properties of gepirone, the manufacturer has stopped the development of gepirone. Also the development of other serotonergic substances with potential antidepressant effects such as ipsapirone, flesinoxan and tandospirone has been stopped.

11.15.3 Tachykinin receptor antagonists

The peptide family of tachykinins (Stout et al., 2001), in particular substance P (SP), have drawn attention to new developments within antidepressant pharmacotherapy (Kramer et al., 1998; Stout et al., 2001). The tachykinin NK₁ receptor is the receptor for SP, which is colocalized with monoamines in several regions of the CNS (Stout et al., 2001). Furthermore, intracerebroventricular administration of SP causes increased concentrations of catecholamine and it has been shown that NK₁ receptor knockout mice exhibit reduced anxiety and stress-related behavior (Stout et al., 2001). In addition a stimulation of an enhanced hippocampal neurogenesis, an effect observed also after application of established antidepressants, has been reported (Kramer et al., 1998; Stout et al., 2001). Despite the fact that several synthetic NK₁ receptor antagonists are available (Stout et al., 2001) only the results of clinical trials with two substances have been published. In a double-blind study an NK₁ antagonist was compared to SSRI treatment and showed superiority in comparison to placebo (Kramer et al., 1998). The scores of both Hamilton depression and anxiety rating scales were reduced significantly. In a

further study no superiority of MK 869 over placebo could be demonstrated. A subsequent substance was examined and a significant, but relatively small superiority in reducing HAM-D scores in comparison to placebo was found (Kramer, 2002). In addition a recent study confirmed antidepressant properties of an additional NK₁ antagonist (Kramer et al., 2004), but this first promising antidepressant approach was not confirmed by clinical data in further studies. Therefore due to these uncertainties there is need to replicate the described findings, but nevertheless NK₁ antagonism seems to be a promising new antidepressant treatment principle with a so far excellent tolerability profile. Up to now the first NK₁ antagonist has been approved by the authorities not as an antidepressant, but as an antiemetic acting substance.

11.15.4 Treatment strategies influencing the hypothalamic pituitary adrenal (HPA) system

11.15.4.1 *CRH₁ receptor antagonists*

Up to now, one CRH₁ receptor antagonists has been investigated in depressed patients. In an open trial examining the safety and tolerability of this compound in 20 depressed patients, which was not designed to test the efficacy, a distinct reduction of the HAM-D and HAM-A scores could be seen within four weeks of treatment (Zobel et al., 2000). The activity of the HPA system was not altered after administration of the CRH₁ receptor antagonist. This indicates that the compound blocked selectively CRH₁ receptors while the HPA system is also under control of CRH₂ receptors. After tapering off of the study medication a certain deterioration of the depressive syndrome was found. The compound was withdrawn from further development because of increased liver enzymes in routine laboratory screening. Due to the lack of placebo-controlled double-blind studies further clinical trials using other CRH₁ receptor antagonists are required to clarify the possible antidepressant potential of these substances.

11.15.4.2 *Steroid synthesis inhibitors*

Inhibitors of steroid synthesis such as ketoconazole or metyrapone have been reported to exert antidepressive effects. Case series and open trials reported antidepressant effects of the fungicide ketoconazole (Anand et al., 1995; Ghadirian et al., 1995; Murphy, 1991; Sovner et al., 2002; Thakore et al., 1995; Wolkowitz et al., 1993). In a placebo-controlled study hints for a putative antidepressant efficacy of ketoconazole were found only in hypercortisolemic but not in normocortisolemic patients (Wolkowitz et al., 1999a). Another placebo-controlled double-blind study in therapy-resistant patients has shown no sufficient antidepressant efficacy (Malison et al., 1999). Similar antidepressant effects have also been shown for metyrapone in case reports and open trials (Ghadirian et al., 1995; Murphy et al., 1991; Murphy, 1991; Raven et al., 1996). In addition, placebo-controlled double-blind studies have been published. In a study in 8 patients, a reduction of the score of the Montgomery-Åsberg depression rating scale (MADRS) of more than 50% within two weeks of treatment has been described (O'Dwyer et al., 1995). Using metyrapone in comparison to placebo in addition to a serotonergic antidepressant therapy a significant accelerating of antidepressant effects could be seen (Jahn et al., 2004). Nevertheless, a definite proof for antidepressant properties of ketoconazole and metyrapone is missing.

A further limitation of the therapy with steroid synthesis inhibitors is the risk of development of adrenal gland insufficiency and a substitution of hydrocortisone may be necessary during the treatment (O'Dwyer et al., 1995). Nevertheless, at least in hypercortisolemic and severely depressed patients, this experimental therapeutic approach can be considered in case of severe treatment resistance.

11.15.4.3 *Neuroactive steroids*

Neuroactive steroids modulate neurotransmitter receptors (Rupprecht et al., 1999) and show antidepressant and anxiolytic properties in animal studies (Bitran et al., 1991; Khisti et al., 2000). Antidepressants, in particular SSRI, enhance the concentrations of endogenous 3α -

reduced neuroactive steroids within different areas of the brain (Rupprecht et al., 1999). These mechanisms possibly may play a role in antidepressant treatments. However, synthetic analogues of 3α -reduced neuroactive steroids for the therapy of psychiatric disorders in humans are not yet available.

Dehydroepiandrosterone (DHEA) is a neuroactive steroid which displays both antagonistic properties at GABA_A receptors and antiglucocorticoid effects (Rupprecht, 1997; Rupprecht et al., 1999; Wolkowitz et al., 1999b). One open study (Wolkowitz et al., 1997) suggested possible antidepressant effects of DHEA. A first placebo-controlled double-blind study was performed using an add-on treatment of DHEA in depressed patients showed a significant reduction in HAM-D scores in DHEA-treated patients (Wolkowitz et al., 1999b). On the contrary in depressed patients DHEA concentrations were found to be enhanced in comparison to healthy volunteers (Heuser et al., 1998), which seems to contradict the indication of DHEA as treatment option in depressive disorders.

11.15.4.4 Glucocorticoid receptor antagonists

Synthetic glucocorticoid receptor antagonists block the effects of cortisol at glucocorticoid receptors. The glucocorticoid-/progesterone-receptor antagonist mifepristone, used in some countries for the termination of first-trimester pregnancy, in first casuistic studies improved depressive symptoms in antidepressant-resistant patients (Murphy et al., 1993). An open label study in patients with psychotic MDD has shown a marked reduction in the Brief Psychiatric Rating Scale (BPRS) scores in the majority of the patients (Belanoff et al., 2002). The symptom amelioration could be seen after seven days of treatment in high-dose treatment groups. A placebo-controlled case series in five patients suffering from psychotic depression showed a HAM-D score reduction up to 26% (Belanoff et al., 2001). However, because of the antagonistic effects of mifepristone at progesterone receptors, the use of this substance as an antidepressant seems to be limited. Further investigations using the

selective glucocorticoid receptor antagonist Org 34517 have been performed. First clinical experiences support the possible antidepressant efficacy of glucocorticoid receptor antagonists. Nevertheless, the results of placebo-controlled double-blind studies of sufficient power and over a sufficiently long treatment period have to be awaited before the question of the antidepressant potential of these substances can be assessed reliably.

12 Pharmacological maintenance therapy

12.1 *Continuation treatment*

The need for continuation treatment has also been clearly demonstrated by placebo-controlled studies. Relapse rates ranged from 31 to 80% for remitted patients who were switched to placebo compared with 0- 31% of those who received active tricyclic medication (Prien et al., 1986; Prien, 1990). Studies with SSRI continuation, amineptine, nefazodone and reboxetine have been completed with similar results. In a systematic review by Hirschfeld (Hirschfeld, 2001) it was found that approximately one-third to a half of patients successfully stabilized in acute-phase treatment will relapse if medication is not sustained throughout the continuation period, and only 10-15% will relapse if medication is continued. Therefore, it is recommended to continue the successful initial antidepressant or combination treatment at the same dose during the continuation phase (Thase, 1999b). For patients who remitted on antidepressant together with lithium as augmentative treatment, combined treatment during continuation has been suggested to be more efficacious than the antidepressant alone (Bauer et al., 2000; Bschor et al., 2002).

Although usually cited as compelling evidence for prophylactic treatment the meta-analysis of Geddes et al. (Geddes et al., 2003) has a stronger focus on continuation treatment and prevention of early relapse. Of the 31 randomized trials included in this metaanalysis, most trials were of 12 months duration and were conducted in acute responders to antidepressant treatment. Thus, they are truly continuation treatment studies. However, a few studies lasting up to three years also support the persistence of effectiveness.

Although not true in the majority of patients, some studies have suggested destabilization of patients under continuous antidepressant treatment (see (Hirschfeld, 2000)). However, at the end of his review Fava concluded that “at present we have no sound data that antidepressant drugs may worsen the course of depression and, if they do, whether the phenomena is

generalized or very limited.” Thus, unless the individual history of a patient shows evidence for negative effects of long-term antidepressant treatment, continuation therapy should be offered to every patient after recovery from a depressed episode. The situation may be different in other subtypes of depression, e.g., bipolar depression with a rapid cycling course; however, these special conditions are beyond the scope of this review.

12.2 Prophylactic treatment

The ultimate goal in any psychiatric disorder is to prevent recurrence of acute symptomatology and improve functionality and quality of life in patients. Clearly, this is not different in unipolar depression. The prophylactic effect of continuing antidepressant medication has been shown in a multitude of studies (Geddes et al., 2003; Hirschfeld, 2000), (see Figure 4).

Figure 4

Cochrane metaanalysis on the efficacy of antidepressants in the recurrence prevention of unipolar depression; risk of relapse, odds ratios by drug type (from (Geddes et al., 2003))

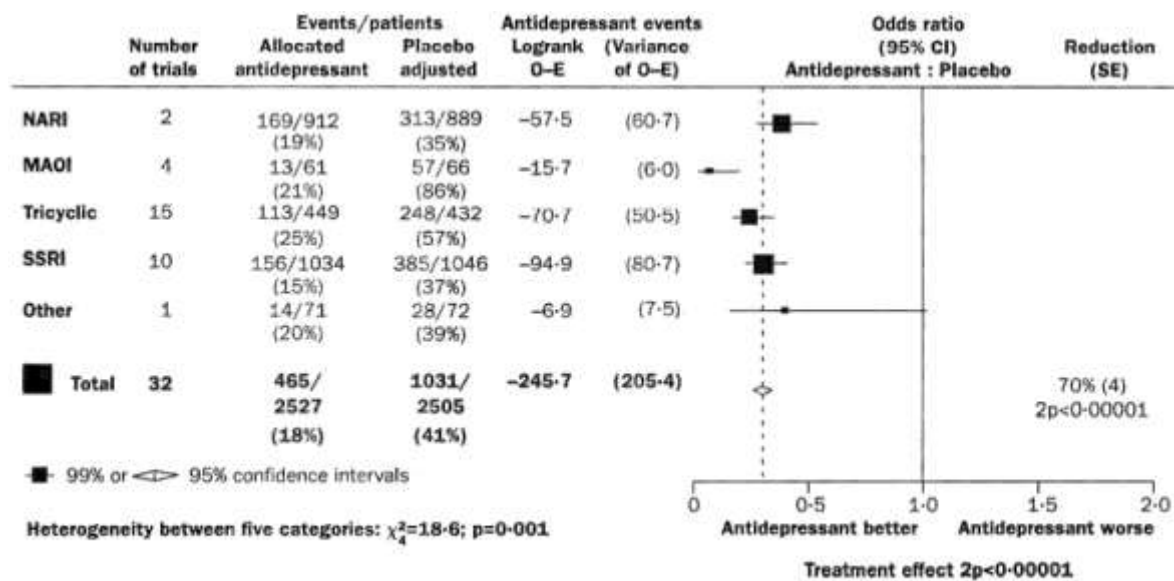


Figure 1: Risk of relapse: odds ratios by drug type

NARI=noradrenaline (norepinephrine) reuptake inhibitor, MAOI=monoamine oxidase inhibitor, SSRI=selective serotonin reuptake inhibitor.

As already detailed in the chapter on “Goals of treatment”, long-term prophylactic treatment after continuation treatment is recommended in patients with a history of recurrent episodes. Besides preventing relapses, antidepressants may add additional value by their neuroprotective properties (Sheline et al., 2003). Taken together, approximately 60% of patients at risk will experience a recurrent episode of depression within one year if untreated, whereas those who continue treatment will have a recurrence rate of between 10% and 30% (Hirschfeld, 2001). If in doubt about the indication for maintenance treatment, an earlier decision in favor of long term maintenance may improve long term outcome: Solomon (Solomon et al., 2000) showed that the risk of a new episode increases by 16% with each successive recurrence. If the patient had a history of at least two (Paykel et al., 1992) or three episodes (Prien et al., 1984), prophylactic treatment is recommended. Guidelines agree that maintenance dosages should be similar to acute and continuation treatment unless tolerability problems force to reduce the medication.

Of the 31 studies included in the meta-analysis by Geddes et al. (Geddes et al., 2003) five studies had a duration of three years and six a duration of two years. However, most of these patients included only a small number of patients and thus do not allow firm conclusions by themselves. Of the randomized controlled studies, the study by Prien et al. (Priem et al., 1984) comparing imipramine and lithium alone or in combination against placebo supplied good evidence both for the prophylactic efficacy of the antidepressant and lithium. The efficacy of imipramine is also supported by a 36 months study of Frank et al (Frank et al., 1990). Similar evidence for continuing prophylactic efficacy has been supplied for nortriptyline (Reynolds, III et al., 1999), sertraline (Keller et al., 1998) and citalopram (Klysner et al., 2002) as well as for the MAO inhibitor phenelzine (Robinson et al., 1991).

12.2.1 Alternatives to long-term antidepressant treatment

12.2.1.1 Lithium

If patients are not responsive to prophylactic antidepressant treatment or do not tolerate side effects, the first alternative is long-term lithium maintenance therapy. Although it may be even more efficacious in bipolar disorder, the efficacy of lithium in preventing relapses in unipolar recurrent depression has been well established (Coppen, 2000; Dunner, 1998; Paykel, 2001; Schou, 1995). This is also supported by two metaanalyses showing that lithium is more effective than placebo in preventing recurrence of unipolar depression (Angst et al., 2002a; Souza et al., 1991). Besides preventing new episodes, lithium has also been demonstrated to normalize the increased mortality rates for cerebrovascular and cardiovascular disorders in affectively ill patients (Angst et al., 2002a) and to reduce the risk of suicide (Angst et al., 2002a; Souza et al., 1991). For a recent up-to-date review see also Müller-Oerlinghausen et al. (Müller-Oerlinghausen et al., 2006). In addition, potential neuroprotective effects including preventive effects against Alzheimer's dementia can be of interest when prescribing long-term lithium prophylaxis. The usually recommended serum lithium levels for prophylaxis in

unipolar recurrent depression are 0.5 to 0.8 mmol/L, but individual variations may occur. The use of extended release forms of lithium has been strongly encouraged as these enable once daily dosing and are associated with less side effects, both favoring enhanced treatment adherence of patients.

12.2.1.2 Anticonvulsants in the prophylaxis of unipolar depression

Carbamazepine has been studied in two small double-blind comparator trials with lithium in recurrent major depression (Angst et al., 2002a; Rush, 1999). Both studies suggested equal efficacy for lithium and carbamazepine. However, when using carbamazepine in prophylactic treatment, its propensity to induce not only its own hepatic metabolism, but also to accelerate metabolism of drugs using CYP 3A4 has to be kept in mind. Some antidepressants, e.g., venlafaxine, nefazodone, reboxetine and imipramine are substrates of CYP 3A4 and thus may not achieve sufficient plasma levels when used in combination with carbamazepine. CYP_{1A2} and CYP_{2C9}, which contribute also to carbamazepine metabolism may also be inhibited by fluvoxamine. Thus, with its potential interactions and a lack of scientific evidence from placebo-controlled studies, carbamazepine can only be recommended as a subordinated choice when other strategies have failed.

For other anticonvulsants only anecdotal reports and small case series have been published for prophylaxis in unipolar depression, but no controlled studies.

As a general recommendation, prophylactic treatment of unipolar depression is not only restricted to pharmacotherapy. Maintaining a good doctor-patient relationship, monitoring adherence and psychoeducation are important as well. To prepare patients and their relatives for long-term prophylactic treatment they should be informed especially about topics as expected course of illness, treatment options, medication efficacy and side effects, use of a daily self-reporting instruments for mood to detect early warning signs of relapse or recurrence, long-term perspectives and, if applicable, projected end of treatment. Patients

should also be trained to distinguish between spontaneous, short-lasting mood-fluctuations (blips) and true emergence of a new episode which should be treated as soon as possible (Rush, 1999). In addition, psychotherapy, especially interpersonal therapy and cognitive behavioral therapy, should be included in the overall treatment portfolio (Baghai et al., 2006). However, a detailed description of the proven efficacy of psychotherapy in addition to medication is beyond the scope of this review.

13 Suicidality and antidepressants

Suicide is the ubiquitous threatening and most deleterious outcome of depression. Suicide rates in depressed patients in longer (>10 years) follow-up studies range from 4 to 10.6% (Angst et al., 2005). A meta-analysis of 27 mortality studies by Inskip (Inskip et al., 1998) using contemporary data and modern analysis techniques led to an estimate of a lifetime suicide risk of 6% for affective disorders. Another metaanalysis by Harris and Barraclough (Harris et al., 1998) found a standard mortality ratio (SMR) of 21.24 for major depressive disorder which was even exceeding the one calculated for bipolar patients. Giving a representative estimate of suicide mortality may be difficult due to methodological shortcomings as outlined by Jules Angst (Angst et al., 2005):

- Selection of the most severely ill, hospitalized patient samples which are not representative.
- Lack of life-long follow- up studies
- The diagnoses in representative suicide samples are retrospective
- In order to compensate for the lack of decade long follow-up studies, risk estimates are based on exposure years assuming an unproven time-related linear risk and
- Perhaps the most significant methodological problem: the uncertain demarcation between bipolar disorder and depression arising from an under-diagnosis of hypomania leading to an underestimate of bipolar II-disorder.

The probably most conclusive prospective long-term, large cohort study on suicide risk in affective disorders was conducted by Angst following up 406 mood disorder patients from 1963 to 2003 (Angst et al., 2005). By 2003, 11.1% of these patients had committed suicide with the highest SMR of 26.4 for unipolar depressed patients. These data underline the prominent role of early diagnosis and treatment of depression for suicide prevention.

Early diagnosis and public awareness have been proven to be effective tools in reducing suicide attempts and completed suicides in large, population based studies. For example, the “Nürnberger Bündnis gegen Depression” (Nuremberg Alliance against Depression) is a community based, multi-faceted, 2-years–intervention focussing on depression. The number of suicidal acts (fatal and non-fatal suicide attempts) showed a significant and clinically relevant reduction compared both to a one-year baseline and a control region (minus 24%) (Althaus et al., 2006; Hegerl et al., 2006).

When depression has been diagnosed, effective pharmacological treatment is the most efficacious way to reduce the risk of suicide. A multitude of epidemiological studies demonstrated reduction of suicidality in regional populations in association with antidepressant prescription (Carlsten et al., 2001; Hall et al., 2003; Ohberg et al., 1998; Rihmer et al., 2000), for a short overview see (Isacsson et al., 2005b; Yerevanian et al., 2004). As suicide is fortunately a rare outcome in controlled studies, it cannot be reliably assessed. However, a secondary analysis by Möller of a six week double-blind controlled study comparing paroxetine and amitriptyline showed a marked reduction in suicidal thoughts for both medications (Möller et al., 1998). Similarly, Szanto (Szanto et al., 2003) demonstrated a complete remission of suicidal ideation in elderly depressed patients after 12 weeks of either amitriptyline or paroxetine treatment. A review of data from several controlled studies by Möller (Möller, 2003) also demonstrated a greater benefit of SSRIs compared to placebo in reducing suicidal ideation.

Still there is some controversy in the appreciation of a causal relationship between antidepressant use and suicidality. Different from the opinion in most other countries, the US Food and Drug Administration (FDA) issued in March 2004 a warning to physicians and patients of an increased risk of suicidality with ten newer antidepressant drugs. There was some notion from controlled studies that SSRIs may cause - very rarely - a higher suicide risk (Healy et al., 2003). This risk seemed to be especially increased in juveniles and adolescents

and led to a still ongoing discussion (for detailed information please refer also to chapters 9.2.1.6) . Following up on this warning, Simon et al. (Simon et al., 2006) analyzed computerized health plan records from altogether 82285 episodes of antidepressant treatment between January 1st 1992 and June 30th 2003. Identifying death by suicide and serious suicide attempts, they found that the risk of suicide attempts was highest in the months before starting antidepressant treatment and declined progressively after starting medication, not being significant higher in the months after starting medication than in subsequent months. Comparing the ten newer antidepressants included in the FDA Black Box warning with older antidepressants, an increase in the risk of suicide was even more likely with the older drugs than with the newer antidepressants. In addition, a recent combined analysis of all placebo-controlled depression and anxiety studies with escitalopram could not find any signal for an increased suicide risk with active medication treatment. On the contrary, suicidal ideation as measured with the item 10 of the MADRS became significantly lower from week 1 onwards with active treatment (Pedersen, 2005).

Another important argument against increased suicide rates with SSRI is provided by the controlled toxicological analysis of all suicide victims over the time period of 8 years in Sweden showing that SSRI are under-represented and that in suicide victims under the age of 15 (n=52), 7 different antidepressants but no SSRI were found (Isacsson et al., 2005a). Besides antidepressants, also other medications including lithium and antipsychotics may significantly reduce suicides in mood disorder patients as demonstrated by the study of Angst (Angst et al., 2005). For antidepressants, the SMR decreased from 33.3 in untreated depressives to 13.8 ($p<0.05$). Weighing risks against benefits of antidepressants, it also has been argued that overdosing of antidepressants is potentially lethal and thus it may be risky to supply a depressed patient with a potential mean of suicide. Besides the fact, that especially newer antidepressants show a large safety margin that makes lethal intoxication difficult, it had been demonstrated in several studies that prescribed medication is not commonly used as

a mean of suicide (Bradvik et al., 2005; Henriksson et al., 2001; Isacson et al., 1997). In addition, it had been demonstrated that the rate of fatal toxicities of antidepressants declines with the introduction of the newer antidepressants and the decreased use of older tricyclics (Morgan et al., 2004).

In summary, it becomes evident that antidepressants are one of the most valuable tools in preventing suicides in depression; although already rare, the risk of lethal intoxication with antidepressant still declines with the replacement of the classical antidepressants with newer agents. Potentially premature actions such as the March 2004 FDA Black Box Warning may cause more harm than benefit for depressed patients.

14 Antidepressant drugs in the treatment of anxiety disorders

The proven efficacy of antidepressant drugs in relieving anxiety symptoms in patients with depressive disorders naturally led to investigations of their potential to relieve symptoms and reduce associated disability in patients with anxiety disorders, including generalized anxiety disorder (GAD), panic disorder, social phobia (also known as social anxiety disorder), post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). In clinical practice, the need for treatment should be determined by the severity and persistence of symptoms, and the level of disability and impact on social functioning; choice of treatment is influenced by patient characteristics (such as previous response, concomitant medication and contraindications), the evidence base supporting its use, patient and physician preference, and the local availability of the proposed intervention (Baldwin et al., 2005b).

14.1 Generalized Anxiety Disorder

In GAD, systematic reviews and placebo-controlled randomized controlled trials (RCTs) indicate that some SSRIs (escitalopram, paroxetine and sertraline), the SNRI venlafaxine, and the TCA imipramine are all efficacious in acute treatment (Baldwin et al., 2005b; Mitte et al., 2005). The small number of comparator-controlled studies reveals no consistent differences in efficacy between active compounds (Mitte et al., 2005). Psychological symptoms of anxiety may respond better to antidepressant drugs than to benzodiazepines (Baldwin et al., 2005b). Double-blind studies in patients who have undergone acute treatment indicate that continuing with an SSRI or SNRI is associated with a further increase in overall response rates. Relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (escitalopram or paroxetine), compared to switching to placebo, for up to six months (Baldwin et al., 2005b). When delivered singly, pharmacological or psychological treatments have broadly similar efficacy in acute treatment,

but the comparative efficacy of drug and psychological approaches over the long-term is not established. It is uncertain whether combining drug and psychological treatments is associated with greater efficacy than with either treatment given alone (Baldwin et al., 2005b).

14.2 Panic disorder

Randomized double-blind placebo-controlled trials of antidepressants indicate that all SSRIs, some TCAs (clomipramine, imipramine), the SNRI venlafaxine and the selective noradrenaline reuptake inhibitor reboxetine are efficacious in acute treatment. Comparator-controlled studies provide some evidence for the efficacy of mirtazapine and moclobemide. The side effect burden associated with SSRI treatment in panic disorder is somewhat less than with other classes of psychotropic drug (Baldwin et al., 1998). After acute treatment, continuing with SSRI or clomipramine is associated with an increase in overall response rates, and placebo-controlled and other relapse-prevention studies in patients who have responded to acute treatment reveal a significant advantage for staying on active medication (fluoxetine, paroxetine, sertraline, imipramine) compared to switching to placebo, for up to six months (Baldwin et al., 2005b). Pooled analyses and RCTs indicate that drug and psychological treatments, delivered singly, have similar efficacy in acute treatment, but suggest CBT may be superior to TCAs in preventing symptomatic relapse (van Balkom et al., 1997). It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment given alone (Barlow et al., 2000; van Balkom et al., 1997).

14.3 Social phobia

Systematic reviews and placebo-controlled RCTs indicate that a range of antidepressants are efficacious, including most SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), the SNRI venlafaxine, the MAOI phenelzine, and the RIMA moclobemide. Double-blind studies indicate that continuing SSRI or SNRI treatment from 12 weeks to 24

weeks is associated with an increase in overall treatment response rates. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on antidepressant medication (escitalopram, paroxetine, sertraline), compared with switching to placebo for up to six months (Baldwin et al., 2005b; Blanco et al., 2003). When delivered singly, pharmacological and psychological treatments have broadly similar efficacy in acute treatment, but acute treatment with cognitive therapy may be associated with reduced risk of symptomatic relapse at follow-up. It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone (Baldwin et al., 2005b; Blanco et al., 2003).

14.4 Post-traumatic stress disorder

Randomized placebo-controlled trials provide evidence for the efficacy of some SSRIs (fluoxetine, paroxetine, sertraline), the SNRI venlafaxine, the TCAs amitriptyline and imipramine, the MAOI phenelzine, and mirtazapine on some outcome measures (Baldwin et al., 2005b; Stein et al., 2000). After a response to acute treatment, continuing with venlafaxine or sertraline treatment over 6 months is associated with a gradual increase in overall treatment response. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication, for fluoxetine (Davidson et al., 2005; Martenyi et al., 2002) and sertraline (Davidson et al., 2001). The comparative efficacy of psychological and pharmacological treatments, in either acute or long-term treatment is uncertain (Baldwin et al., 2005b).

14.5 Obsessive-compulsive disorder

Systematic reviews and meta-analyses of randomized placebo-controlled trials indicate that the TCA clomipramine and the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) are efficacious in acute treatment. The efficacy of clomipramine

appears marginally superior to that of SSRIs in meta-analysis (Ackerman et al., 2002), but the tolerability of SSRIs is generally superior (Fineberg et al., 2005). Fixed-dose comparator studies provide inconsistent evidence for a dose-response relationship with SSRIs, higher doses being associated with greater efficacy in some but not all evaluations (Fineberg et al., 2005). Long-term (up to 12 months) double-blind studies show an advantage for continuing with medication in patients responding to acute treatment. Most relapse-prevention studies in patients who have responded to acute treatment reveal a significant advantage for staying on active medication (clomipramine; paroxetine; sertraline; and fluoxetine, at higher dose), compared to switching to placebo (Fineberg et al., 2005). Combining treatment approaches may be superior to psychological approaches or serotonergic antidepressant treatment given alone. The evidence for enhanced efficacy of exposure therapy with clomipramine compared to exposure alone is inconsistent, but fluvoxamine has been shown to enhance the efficacy of exposure therapy and CBT. Relapse rates may be greater after initial treatment with a pharmacological rather than a psychological intervention (Simpson et al., 2004).

15 Other treatments

15.1 Psychotherapy¹³

15.1.1 CINP consensus statement for psychotherapy treatment options

Empirically supported psychotherapies are potent alternatives to and augmenters in combinations with antidepressant medications. Efficacious psychotherapies may have particular benefits for depressed patients, such as pregnant women, who prefer to avoid medication. In non-industrialized countries, such psychotherapies may be the only feasible, affordable treatments for depression (Bolton et al., 2003).

Interpersonal psychotherapy (IPT) is a time-limited, diagnosis-focused treatment shown in repeated randomized controlled trials to have efficacy as both an acute and a maintenance treatment for major depressive disorder (Weissman et al., 2000). IPT defines depression as a treatable medical illness that is not the patient's fault. It focuses on the connection between the patient's mood and interpersonal life circumstances. It has been shown not only to relieve depressive symptoms but to build social skills. IPT has shown more modest benefit for dysthymic disorder (Browne et al., 2002; Markowitz et al., 2005). One large trial has indicated the efficacy of an adaptation of IPT (Interpersonal Social Rhythms Therapy) as an adjunctive treatment for bipolar disorder (Frank et al., 2005). Other studies have found that interpersonal counseling (IPC), a short, dilute version of IPT, relieves symptoms of subsyndromal depression (Weissman et al., 2000).

On the basis of its performance in controlled efficacy trials, interpersonal psychotherapy, along with cognitive therapy and behavioral therapies (CBT), should be included in algorithms of standard treatment for depressive disorders. IPT and cognitive behavioral

therapies have already been included in numerous professional and national treatment guidelines (e.g., (Karasu et al., 1993)).

15.2 Electroconvulsive Therapy (ECT)¹⁴

Electroconvulsive therapy is the safe induction of a series of generalized epileptic seizures for therapeutic purposes using brief-pulse stimulation techniques under anesthesia and muscle relaxation. Informed consent of the patient or the responsible legal guardian is mandatory. Since the first publications the excellent therapeutic effectiveness of this method has been described in extensive studies (Abrams, 2002; Baghai et al., 2005; ECT review group, 2003).

15.2.1 ECT as first line treatment

In case of refusal of food and drinking and severe psychomotor retardation ECT has shown to be one of the safest therapeutic options with the fastest relief of symptoms (Gangadhar et al., 1982). Therefore depressive stupor and inanition as in melancholic and/or psychotic depression can be a first line indication for ECT before other treatments are prescribed. If due to other conditions, e.g. severe psychotic symptoms and/or high suicide risk, a rapid improvement is crucial for the patient ECT should be considered earlier than other therapeutic options (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In psychotic depression, the remission rate for ECT approximates 90%, with relief experienced within 10 to 14 days (Petrides et al., 2001). The risks of suicide that mark severe psychiatric illnesses are quickly relieved by ECT, although attention to continuation treatments is essential to sustain the benefit (Kellner et al., 2005). Also other acute psychiatric syndromes such as severe excitement e.g. in delirious mania and malignant catatonia that mark systemic illnesses as lupus erythematosus, a neuroleptic malignant syndrome and medication toxicity may require ECT as a first line treatment (Abrams, 2002; Baghai et al.,

¹⁴ See chapter 18.2 for more detailed information in Annex 2 - Additional information on Electroconvulsive Therapy

2005). Intensive ECT, usually administered daily (en bloc), relieves the high rates of mortality associated with malignant catatonia and delirious mania (Fink, 1999; Fink et al., 2003). In addition, when depression, mania, and psychotic symptoms accompany systemic illnesses or are present during early pregnancy or the post-partum breast-feeding period, the administration of medications are often precluded and ECT becomes a useful treatment option. In the case of severe and life threatening adverse events of antidepressants and in psychotic depressed patients also in case of severe adverse events due to neuroleptics, ECT monotherapy can be a safe first-line treatment. This is also true for patients suffering from severe somatic diseases including the risk of worsening due to antidepressant and antipsychotic pharmacotherapy (Beliles et al., 1998; Franco-Bronson, 1996; Rothschild, 1996). In addition due to both, a long duration and a chronic course of the index episode are negative outcome predictors in depressive disorders concerning a higher risk for therapy resistance against medication and ECT (Beliles et al., 1998; Prudic et al., 1990), more patients than today should be informed about these possible response rates to be involved properly in a shared decision making concerning their antidepressant treatment. Nevertheless the primary use of ECT is handicapped by the severe stigma and even legal restrictions against its use in some jurisdictions (Ottoson et al., 2004). Individual signed consent is required before using ECT treatment. Patients in stupor, manic excitement, catatonic mutism, and acute paranoid states may not be able to offer written consent and alternative consent processes which vary with jurisdictions in different countries must be applied as described before. It is useful for practitioners, who are responsible for the more acute and severely ill psychiatric patients, to consider ECT as a primary indication and to be acquainted with all the means for proper consent for treatment within their jurisdiction.

15.2.2 ECT as second line treatment

The most common use of ECT is in patients to whom medications have failed to elicit remission or in whom medication toxicity interrupted the course of therapy (Abrams, 2002; Baghai et al., 2005). Nevertheless patients receive ECT rarely after the first two medication treatment failures often used as a criterion for *pharmacotherapy resistance* (Möller, 1997; Prudic et al., 1996; Sackeim, 2001; Warneke, 1993). The utilization of ECT enhances response rates significantly (Davidson et al., 1978; Folkerts et al., 1997; Kroessler, 1985). This is especially true in patients suffering from psychotic depression, even if antipsychotic therapies have been applied adequately before (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Folkerts et al., 1997). Intolerable side effects of antidepressant medications, somatic comorbidities emerging during the pharmacological treatment (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Rasmussen et al., 2002) or worsening of depressive symptoms including severe suicidality during an antidepressant pharmacotherapy can be also the cause of initiating an ECT treatment course (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). First- and second-line indications and rare *last resort* indications are summarized in Table 12.

Table 12

Indications for Electroconvulsive Therapy (adopted from (Baghai et al., 2005))

Category of ECT-Indications	Indication
ECT as a first-line treatment	<ul style="list-style-type: none"> • febrile catatonia* • malignant neuroleptic syndrome* • severe depressive episode** • schizoaffective psychosis** • schizophrenia**, *** • in case of life threatening or intolerable side effects of psychopharmacological treatments
ECT as a second-line treatment	medication treatment failures in: <ul style="list-style-type: none"> • depression • schizoaffective psychosis • schizophrenia • mania • depression or psychotic symptoms in case of organic diseases
ECT as a last resort treatment	<ul style="list-style-type: none"> • treatment resistant obsessive compulsive disorder (OCD) • treatment resistant dyskinesias • treatment resistant Gilles de la Tourette-syndrome • treatment resistant epilepsy • Parkinson's disease (treatment resistant)
* (Fink et al., 2003)	
** with suicidality which can not be handled even on protected wards, psychotic symptoms or depressive stupor, with positive symptoms or acute danger of self harm or harm of others	
*** (Fink et al., 1996b)	

15.2.3 Continuation ECT (C-ECT)¹⁵

As described in chapters 12 and 12.2 besides pharmacologic and psychotherapeutic continuation therapies especially after pharmacotherapy treatment failures, also ECT is an efficacious prophylactic tool (Kellner et al., 2005; Sartorius et al., 2005a; Sartorius et al., 2005b), even if the scientific evidence for use of ECT as a maintenance treatment is limited due to an absence of controlled studies. Continuation ECT should be considered in cases of recurrence of depressive symptoms especially when adequate pharmacologic therapy fails. Even if the prior history of an individual patient shows an enhanced risk for recurrence of

¹⁵ The terms *continuation treatment* and continuation ECT (C-ECT) are predominantly used to characterize the maintenance treatment after successful treatment of the index phase. It is sometimes distinguished from *maintenance treatment* and maintenance ECT (M-ECT) (Sartorius et al., 2005a) due to theoretical considerations about a switch to prophylactic treatment preventing new episodes of depression. Because this time point cannot be defined precisely in an individual patient, in the following text only the term C-ECT is used.

depression during continued pharmacotherapy including both antidepressants and mood stabilizers, C-ECT should be part of the treatment plan (Frey et al., 2001; McCall, 2001; Rabheru et al., 1997). The usual clinical procedure is to prolong the treatment intervals according individual clinical requirements. During the acute treatment a patient usually receives two or three treatment per week. Afterwards usually one treatment per week is applied for four to eight weeks, then one treatment every two weeks and one treatment every four weeks. This frequency should be maintained for at least six months. A frequently used alternative strategy (the so called *cafeteria style*) is the individual decision, whether an C-ECT treatment is administered when the first signs of recurrence of depressive symptoms are reported (Abrams, 2002; Fink et al., 1996a). Regular weekly evaluations help to judge about the necessity to shorten the treatment free intervals on an individual basis. The same evaluation is necessary during the attempt to stop ECT treatment after six month. As soon as depressive symptoms reoccur, a prolongation of the C-ECT should be applied.

15.2.4 Side effects

15.2.4.1 Somatic side effects

The most frequent immediate unpleasant effects of ECT are headache, nausea and vomiting (varying with anesthetic). Headaches and nausea are best treated symptomatically, and if severe, by changing the induction medications. Other rare complications of ECT can be cardiovascular events emerging from anesthesia. On rare occasions, the seizure is prolonged beyond the anticipated 30 to 180 seconds (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). The treating anesthesiologist or psychiatrist will end the seizure by the administration of intravenous benzodiazepines (e.g. diazepam), anesthetics or other anticonvulsants. This event and also the rare case of nonconvulsive seizures are best managed by ictal and postictal EEG monitoring (Grogan et al., 1995).

15.2.4.2 Cognitive side effects

All patients are confused on awakening after a seizure. The duration and the severity of the post-seizure delirium vary with patient age (older patients have more severe and more prolonged periods of confusion), dosage and type of anesthetic, and the characteristics of the medications, both psychoactive and systemic, which may be prescribed for the patients. Special attention is paid to sedatives and anxiolytics, antipsychotics, and lithium that may augment the confusional syndrome.

Typical side effects which are more prominent in bilateral than in unilateral and in high-dose than in lower dose ECT (ECT review group, 2003) are transient cognitive disturbances. The rate of cognitive disturbances is dependent on dose and application of electrical stimulation (Devanand et al., 1991; Krystal et al., 1997). Sometimes patients experience profound and sustained memory loss, sufficient to interfere with their ability to return to work. Such instances are extremely rare but are the principal burden of the complaints against the use of ECT (Abrams, 2002; Ottoson et al., 2004). Nevertheless recent improvements in the use of ECT include methods to maintain the good therapeutic efficacy together with a better tolerability concerning cognitive disturbances. If in spite of these precautions cognitive disturbances occur, a rapid improvement within one and up to four weeks can be observed in most cases (Ghaziuddin et al., 2000). Follow-up investigations showed a complete reversibility of cognitive side effects after an ECT course (Baghai et al., 2005; Ghaziuddin et al., 2000) or even an improvement in comparison to the time interval before ECT treatment (Baghai et al., 2005).

15.2.5 Clinical precautions and special considerations

After many decades of research and clinical experience, clinicians have developed protocols for the safe treatment of patients warranting ECT regardless of age, medical status, or physical state. No absolute contraindications are acknowledged. An individual and interdisciplinary

risk / benefit-analysis is necessary if such risks are present and patients and relatives or responsible legal guardians have to be informed about risk / benefit ratios to contribute to a shared decision. The various conditions requiring special attention described in (Abrams, 2002; Baghai et al., 2005) are summarized in Table 13.

Table 13

Clinical conditions requiring special attention before and during ECT (adopted from (Baghai et al., 2005))

Category	Clinical condition
Enhanced intracerebral pressure*	at present
Cerebral infarction*	not older than 3 month
Myocardial infarction*	not older than 3 month
Intracerebral tumor*	including intracerebral edema
Any life threatening anesthesia risk*	at present
Cardiovascular disorders	cardiac arrhythmias, instable angina pectoris, myocardial infarction (older than 3 month), myocardial insufficiency, heart valve abnormalities, not sufficiently treated hyper- or hypotonia, aortal aneurysm
Medical disorders	disturbance of blood coagulation, severe liver diseases, severe pulmonal diseases, pheochromocytom
Neurological disorders	intracerebral neoplasias, intracranial bleeding, intracerebral vascular malformations, cerebral ischemia, cerebral inflammations, hydrocephalus, dementias, diseases of the basal ganglia, craniotomies, severe cerebral traumas
	osteoporosis
Orthopedic disorders	increased aspiration risk; intubation recommended
Esophageal hernia	if enhancing the ECT risks or reducing ECT efficacy
Concomitant pharmacological treatment	*bold: in former times considered as absolute contraindications; today an individual risk/benefit-analysis is necessary.

15.2.6 Safety

In general ECT is one of the best tolerated antidepressant therapies with low risk for severe complications, even lower than during the application of TCA (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). The mortality rate during ECT varies between 1 : 50,000 and 1 : 25,000 treatments (Abrams, 2002;

American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In less than one in 10,000 treatments severe complications are seen that warrant special attention (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

15.3 Recently developed and other non-pharmacological treatments

15.3.1 Introduction

Beside new pharmacological antidepressant treatment strategies several new biophysical approaches have been under investigation for the treatment of major depressive illness during the last decade: Repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), magnetoconvulsive therapy (MST) and, very recently, deep brain stimulation (DBS). These methods have in common that they directly or indirectly target brain regions that play a role in the pathophysiology of major depression. All methods except MST differ from electroconvulsive therapy (ECT) regarding their presumed mechanisms of action, though they have often been discussed in comparison with ECT. rTMS, VNS, MST and DBS have been developed in a hypothesis driven manner based on the current view of major depression being a cerebral disorder and affecting integrated pathways linking select cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators (Padberg et al., 2003). However, these brain stimulation methods use different “windows” to access the anatomically defined pathways showing functional changes during the acute episode and attempt to modulate the system in the direction of a normal regulation of mood and emotions. rTMS is currently mainly targeted to cortical prefrontal sites (George et al., 2003; Padberg et al., 2003), whereas VNS enters the system by vagal afferents to the vagal nucleus and the nucleus tractus solitarius in the brain stem, that are linked to regions of the brain involved in mood regulation such as the amygdala, the hippocampus, and the locus coeruleus (George et al., 2003).

MST utilizes the ECT approach of inducing generalized therapeutic convulsions in order to treat depression. However, the method attempts to be more focal compared to ECT to minimize side effects and particularly exerts its effect on frontal and prefrontal cortical and subcortical sites (Lisanby et al., 2003b). Very recently, interesting data have been presented using DBS for the stimulation of a subgenual cingulate region (Brodmann area 25) which is metabolically overactive in treatment resistant depression and show a normalization in activity after recovery (Greenblatt et al., 1964; Lisanby et al., 2003b). However, also other regions in the basal ganglia and their pathways to prefrontal limbic areas may be putative targets in future studies.

Psychosurgical interventions as stereotactically applied bilateral orbitomedial lesions for resistant severe depression are pointing in the same direction, however, are of marginal clinical significance nowadays (Sachdev et al., 2005). Moreover, moxibustion has also to be mentioned among physical treatment options for depression, however, empirical data are insufficient and it mainly plays a role in the traditional Chinese medicine (Cheng et al., 2005).

15.3.2 Magnetic seizure therapy (MST)

MST is a variant of repetitive transcranial magnetic stimulation (rTMS) utilizing stronger stimulation parameters (40 % more intensity compared to standard rTMS stimulation, higher frequency and a prolonged impulse about 0.4 ms) compared to conventional rTMS in order to intentionally induce an epileptic seizure for therapeutic purposes. It is hypothesized that MST might be a kind of convulsive therapy that retains the therapeutic efficacy of ECT with an improved side effect profile as MST should induce a secondary generalized seizure more focally in relevant brain regions (Lisanby et al., 2003b) as the magnetic field can penetrate scalp and skull without hindrance. Animal studies and safety data of clinical pilot studies in depression have been published supporting this notion (Lisanby et al., 2001c; Lisanby et al., 2003a; Moscrip et al., 2005). Its antidepressant efficacy is currently under investigation and so

far only case reports are available (Lisanby et al., 2001a; Moscrip et al., 2005). MST is still at an early stage of development (Lisanby et al., 2003a) and therefore restricted to the use in experimental treatment designs.

15.3.3 Repetitive transcranial magnetic stimulation (rTMS)¹⁶

Transcranial Magnetic Stimulation (TMS) has been originally introduced in 1985 by Barker et al. as a non-invasive tool to electromagnetically stimulate the primary motor cortex in humans (Lisanby et al., 2003b) has turned to a powerful research tool in neurophysiology and cognitive neuroscience. As antidepressant intervention rTMS is usually targeted to the dorsolateral prefrontal cortex based on well-replicated findings showing reversible functional changes in this region. In the majority of studies the left prefrontal cortex has been chosen based on the observed asymmetry of prefrontal function associated with major depression (Lisanby et al., 2003b). A large number of different stimulation parameters, e.g. frequency and intensity of stimulation, have been applied in studies (Padberg et al., 2003) and the usual treatment duration has been one to four weeks of treatment.

About 25 randomized, placebo-controlled clinical trials including about 750 patients suffering from major depressive episodes have been conducted to date investigating the safety and efficacy of rTMS as antidepressant intervention (Berman et al., 2000b; Dolberg et al., 2002; Garcia-Toro et al., 2001a; Garcia-Toro et al., 2001b; Kauffmann et al., 2004; Loo et al., 2003; Miniussi et al., 2005; Mosimann et al., 2004; Nahas et al., 2003; Padberg et al., 1999; Padberg et al., 2002; Padberg et al., 2003; Pascual-Leone et al., 1996; Rossini et al., 2005). In the majority of these trials significant placebo/verum differences have been observed with antidepressant effects ranging from modest to substantial. Due to the methodological limitations of many of these trials regarding rather small sample sizes, the difficulty with controlling placebo rTMS and short observation periods, the current assessment of its efficacy

¹⁶ See chapter 18.3 for more detailed information in Annex 3 - Additional information on transcranial magnetic stimulation

is more sober after initial enthusiasm about its treatment potential. Several meta-analyses have been conducted (Berman et al., 2000b; Burt et al., 2002; Couturier, 2005; Dolberg et al., 2002; Ebmeier et al., 2006; Garcia-Toro et al., 2001a; Martin et al., 2003; Pascual-Leone et al., 1996; Schulze-Rauschenbach et al., 2005) supporting the antidepressant efficacy of rTMS, but clinical effects are found to be not very strong and the clinical significance may be questionable. rTMS has also been directly compared with ECT in five parallel design trials (Grunhaus et al., 2000; Grunhaus et al., 2003; Pridmore et al., 2000; Schulze-Rauschenbach et al., 2005) where rTMS has been found to be equally effective compared to ECT in patients suffering from major depressive episodes without psychotic features, but to be inferior in psychotic depression (Grunhaus et al., 2000). Four trials have investigated the combined treatment with active rTMS plus antidepressant compared to sham rTMS plus antidepressant in order to answer the question whether rTMS may augment the effect of antidepressant medication (Lisanby et al., 2001b; Rumi et al., 2005), but only one study where rTMS was combined with amitriptyline found a significant superiority of combined active treatment (Rumi et al., 2005). Apart from single studies and case reports little is known regarding the stability of effects and potential maintenance treatment strategies (Pascual-Leone et al., 1996) and the largest body evidence points to transient effects after completion of rTMS treatment (Pascual-Leone et al., 1996; Schüle et al., 2003). rTMS appears to be safe and well tolerated by patients within a range of parameters defined according to a consensus (Wassermann, 1998).

In conclusion, there is considerable evidence of an antidepressant efficacy of high frequency rTMS over the left dorsolateral prefrontal cortex applied over two to four weeks and rTMS may be applied successfully as adjuvant antidepressant intervention. However, the antidepressant efficacy of rTMS has still not been sufficiently proven due to methodological limitations of previous clinical trials.

15.3.4 Vagus nerve stimulation (VNS)¹⁷

In the 80ies and 90ies of the last century VNS was developed in animal models with regard to its putative anticonvulsant action and has been introduced into the routine treatment of therapy-resistant focal epilepsies about a decade ago including approval by the U.S. Food and Drug Administration (FDA). Theoretical considerations regarding the functional anatomy of the vagus nerve also projecting to areas of the brain relevant for generation and control of mood and emotions, but also observations of mood changes in epilepsy patients undergoing VNS, have triggered the application of VNS in depressive disorders (George et al., 2003). VNS has been investigated in a series of open and controlled clinical trials in depressed patients following an industrial development program, and recently the data of the complete trial set have been published (George et al., 2005; Nahas et al., 2005; Rush et al., 2000; Rush et al., 2005b; Rush et al., 2005a; Sackeim et al., 2001).

The results of an open pilot study (Rush et al., 2000; Sackeim et al., 2001) led to a double-blind randomized placebo-controlled multicenter trial including 235 patients who received either active or placebo stimulation during a ten weeks period (Rush et al., 2005a). After completion of the acute treatment period, all patients received continuous treatment and long-term data has been recently published of 205 patients after 12 months stimulation (Rush et al., 2005b). In the acute study no difference in primary and secondary outcome measures between VNS or placebo treatment groups was observed (Rush et al., 2005a). To allow interpretation of the clinical meaning of the long-term data in terms of efficacy, a post-hoc comparison study with the same inclusion criteria as the controlled VNS study was initiated including 124 patients who received “treatment as usual” (TAU) (George et al., 2005). After twelve months a clinical response was found in 29.8% of the patients included in the VNS study, whereas only 12.5% responded in the TAU study, remission was achieved in 17.1% of the VNS study

¹⁷ See chapter 18.4 for more detailed information in Annex 4 - Additional information on vagus nerve stimulation (VNS)

compared to 6.7% of the TAU study (George et al., 2005). Concerning the safety of VNS the results of the studies in epilepsy were essentially confirmed and VNS carries significant health risks including voice alterations occurred, cough, dyspnoea, neck pain, dysphagia, laryngismus, paraesthesia and pharyngitis (Rush et al., 2005a) which may improve gradually during treatment (Rush et al., 2005b).

Based on the efficacy and safety data the VNS therapy system was recently approved by the U.S. FDA for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. Despite this approval it is not known to date whether VNS exerts antidepressant effects superior to placebo or other treatments and further controlled parallel design long-term trials are urgently needed. Because of its invasive nature VNS should be strictly reserved for exceptional cases where the patient's demand for this treatment is high, other interventions have failed and a clinical benefit is likely.

15.3.5 Deep brain stimulation

Deep Brain Stimulation (DBS) is a well established treatment for intractable Parkinson's disease (PD) and other movement disorders, where usually the subthalamic nucleus, the globus pallidus internus or the thalamus are stimulated (Mayberg et al., 2005). An implantable stimulation system alike the VNS system is used to stereotactically target relevant brain areas and generate a functional lesion in regions that are generators of symptoms of PD and other movement disorders. For the use of DBS in psychiatric disorders only case reports have been published reporting cases of obsessive compulsive disorder or the Gilles de la Tourette syndrome treated with DBS (Mayberg et al., 2005). Very recently, Helen Mayberg and colleagues (Mayberg et al., 2005) published six case of patients treated with DBS of the subgenual cingulate cortex hypothetically driven by their previous studies showing the

consistent involvement of this region in acute sadness in healthy volunteers and antidepressant treatment effects in depressed patients (Kopell et al., 2004; Mayberg et al., 1999; Mayberg et al., 2005). The authors found a striking and sustained remission of depressive symptoms in four of the reported six patients, associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites demonstrated by positron emission tomography (Wu et al., 1990).

DBS treatment is so far only an experimental intervention in depression and further extensive methodological research is needed to develop this approach towards a clinically applicable treatment.

15.3.6 Total or partial sleep deprivation (wakefulness therapy)

Total sleep deprivation (TSD) is a non-pharmacological intervention, which exerts rapid antidepressant effects in about 60% of depressed patients (Wu et al., 1990). Late night sleep deprivation (partial sleep deprivation, PSD) is as effective and rapid as TSD and better accepted by depressed patients (Schilgen et al., 1980). On the contrary early night SD is be ineffective in the treatment of depression (Wu et al., 1990).

Clinical relevance of TSD is limited since relapse after sleep deprivation is a frequent phenomenon observed in most of the patients (Wu et al., 1990). Different strategies for relapse prevention after SD are the combination with lithium (Benedetti et al., 1999; Grube et al., 1990), pindolol (Smeraldi et al., 1999), bright light therapy (Colombo et al., 2000; Neumeister et al., 1996) or the serial administration of PSD up to twice a week (Kuhs et al., 1996; Kuhs et al., 1998). It has been recently shown in several clinical trials that a “phase advance” of the sleep period after SD can be used to prevent relapse in about 60% of responders (Kuhs et al., 1996; Lee et al., 1999). Nevertheless due to the overall lower effectiveness in comparison to other antidepressant treatments and the transient effects sleep deprivation is used in clinical routine predominantly as an augmentation strategy.

15.3.7 Bright light therapy (phototherapy)

In seasonal affective disorders bright white light therapy exerts clear antidepressant effects (Lee et al., 1999; Rosenthal et al., 1985). For other indications such as MDD or bipolar depression further research was considered to be necessary to determine the usefulness of phototherapy (Benedetti et al., 2001; Compton et al., 2000; Prasko et al., 2002). Some studies report a good benefit of depressed patients receiving bright light therapy to augment an antidepressant pharmacotherapy (Benedetti et al., 2003; Loving et al., 2002). In recent reports phototherapy was also suggested as an efficacious adjunctive treatment also in non-seasonal unipolar and bipolar depression (Martiny et al., 2005a; Martiny et al., 2005b; Terman et al., 2005). Nevertheless due to the fact that some reports of the efficacy of light therapy are not based on rigorous study designs, more randomized controlled trials are necessary to evaluate the therapeutic impact of phototherapy on non-seasonal depression adequately (Golden et al., 2005). Because of these in part controversial results, phototherapy is recommended in seasonal depression as a first line therapy, whereas it should be considered in other forms of depression as an augmentation strategy up to now (Craft et al., 2004).

15.3.8 Exercise

A variety of publications have discussed the theoretical background of beneficial effects of physical exercise in treatment of MDD. In addition reviews report about and recommend exercise as a promising behavioral intervention at least as an adjunct treatment of depression (Craft et al., 2004; North et al., 1990). Even long-term changes and antidepressant effectiveness of exercise during 20 weeks of treatment have been reported (Singh et al., 2001). Nevertheless in detailed reviews and a meta-analysis it was published that the effectiveness of exercise in reducing symptoms of depression cannot be determined yet because of methodological weaknesses in all published studies on exercise in MDD so far (Barbour et al., 2005; Lawlor et al., 2001). It therefore has to be stated, that at the present time exercise can

not be recommended to be more than a supplemental therapeutic option during antidepressant therapies. In addition there is some limited evidence to support the effectiveness of yoga breathing exercises as a complementary treatment of depression (Jorm et al., 2002), but the quantity of the possible effectiveness cannot be judged at the present time.

15.3.9 Acupuncture¹⁸

15.3.9.1 Efficacy

Due to the fact that the use of complementary and alternative therapies is overrepresented in patients suffering from depressive syndromes (Kessler et al., 2001), it is necessary to evaluate the actual knowledge about the main therapeutic options in this field. Acupuncture has a long history in the eastern culture and the traditional Chinese medicine describes influence of acupuncture on the balance of health and energy in the human body. Traditional acupuncture involves the insertion of needles into specific trigger points on different parts of the body. Despite a variety of published studies in this field, a recent review describes insufficient evidence to determine the efficacy of acupuncture in comparison to pharmacological antidepressant treatment (Smith et al., 2005). Also adequate blinding of physicians and patients in clinical trials together with standardized outcome measures are necessary before clinical and scientific recommendations can be made (Smith et al., 2005).

15.3.9.2 Safety and tolerability

An overall good safety and tolerability of acupuncture has been described. Especially in trials comparing TCA with acupuncture the typical side effects were much less in the acupuncture groups (American Psychiatric Association, 1994). Studies comparing modern and better tolerated antidepressants are not published up to now.

16 Conclusions and Implications

Placeholder

Conclusions drawn from this technical review will be added after all input from regional conferences and the governing body of CINP have been received, reviewed by the task force and incorporated into the body of text.

17 References

1. Aarre TF and Bugge P. (2002): ECT for patients taking lamotrigine. *Eur. Psychiatry* **17 Suppl 1**, 135
2. Abrams,R. (2002): Electroconvulsive Therapy. Oxford University Press, New York, Oxford
3. Ackerman DL and Greenland S. (2002): Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. *J. Clin. Psychopharmacol.* **22**, 309-317
4. Adli M, Baethge C, Heinz A, Langlitz N, Bauer M. (2005): Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. *Eur. Arch. Psychiatry Clin. Neurosci.* **255**, 387-400
5. Adli M, Berghofer A, Linden M, Helmchen H, Muller-Oerlinghausen B, Mackert A, Stamm T, Bauer M. (2002): Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: results of a 2-year observational algorithm study. *J. Clin. Psychiatry* **63**, 782-790
6. Adli M, Rush AJ, Moller HJ, Bauer M. (2003): Algorithms for optimizing the treatment of depression: making the right decision at the right time. *Pharmacopsychiatry* **36 Suppl 3**, S222-S229
7. AHCPR (Agency for Health Care Policy and Research). (1999): Evidence report on Treatment of depression: Newer Pharmacotherapies. AHCPR, Washington DC
8. Aichhorn W, Whitworth AB, Weiss U, Stuppaeck C. (2004): Mirtazapine and breastfeeding. *Am. J. Psychiatry* **161**, 2325
9. Alfonso J, Frick LR, Silberman DM, Palumbo ML, Genaro AM, Frasch AC. (2006): Regulation of hippocampal gene expression is conserved in two species subjected to different stressors and antidepressant treatments. *Biol. Psychiatry* **59**, 244-251
10. Allen JJB and Schnyer RN. (1998): The Efficacy of Acupuncture in the Treatment of Major Depression in Women. *Psychol Sci* **9**, 397-402
11. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lepine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh WA. (2004): Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr. Scand. Suppl.* **21-27**
12. Altar CA. (1999): Neurotrophins and depression. *Trends Pharmacol. Sci.* **20**, 59-61
13. Althaus D, Niklewski G, Schmidtke A, Hegerl U. (2006): [Changes in the frequency of suicidal behaviour after a 2-year intervention campaign.]. *Nervenarzt*

14. Ambrosini PJ. (2000): A review of pharmacotherapy of major depression in children and adolescents. *Psychiatr. Serv.* **51**, 627-633
15. American Diabetes Association. (2003): Economic cost of diabetes in the US in 2002. *Diabetes Care* **26**, 917-932
16. American Psychiatric Association. (1994): Diagnostic and statistical manual of mental disorders. 4rd ed rev. Washington DC
17. American Psychiatric Association. (2000): Practice guideline for the treatment of patients with major depressive disorder (revision). *Am. J. Psychiatry.* **157**, 1-45
18. American Psychiatric Association Committee on Electroconvulsive Therapy, Weiner,R.D., Coffey,C.E., Folk,J., Fochtmann,L.J., Greenberg,R.M., Isenberg,K.E., Kellner,C.H., Sackeim,H.A. & Moench,L.M. (2001): The Practice of Electroconvulsive Therapy. American Psychiatric Association, Washington
19. Amsterdam JD. (2003): A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J. Clin. Psychiatry* **64**, 208-214
20. Amsterdam JD and Shults J. (2005): MAOI efficacy and safety in advanced stage treatment-resistant depression-A retrospective study. *J. Affect. Disord.* **89**, 183-188
21. Anand A, Malison RT, McDougle CJ, Price LH. (1995): Antiglucoctocoid treatment of refractory depression with ketoconazole: a case report. *Biol. Psychiatry* **37**, 338-340
22. Ananth J. (1998): Treatment-resistant depression. *Psychother. Psychosom.* **67**, 61-70
23. Anderson CS, Hackett ML, House AO. (2004): Interventions for preventing depression after stroke. *Cochrane. Database. Syst. Rev.* CD003689
24. Anderson IM. (1998): SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress. Anxiety.* **7 Suppl 1**, 11-17
25. Anderson IM. (2000a): Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J. Affect. Disord.* **58**, 19-36
26. Anderson J. (2000b): On variability of effects for a metaanalysis of rheumatoid arthritis radiographic progression. *J Rheumatol.* **27**, 540-542
27. Andlin-Sobocki P, Jönsson B, Wittchen H-U, Olesen J. (2005): Cost of brain disorders in Europe. *European Journal of Neurology* **12**, S1-S27
28. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, de Graaf R, Vollebergh W, Dragomirecka E, Kohn R, Keller M, Kessler RC, Kawakami N, Kilic C, Offord D, Ustun TB, Wittchen HU. (2003): The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *Int. J Methods Psychiatr. Res.* **12**, 3-21
29. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, Gonzalez-Grande R, Pizarro A, Duran JA, Jimenez M, Rodrigo L,

- Romero-Gomez M, Navarro JM, Planas R, Costa J, Borrás A, Soler A, Salmeron J, Martin-Vivaldi R. (2005): Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* **129**, 512-521
30. Andrews JM and Nemeroff CB. (1994): Contemporary management of depression. *Am. J. Med.* **97**, 24S-32S
31. Anghelescu I, Klawe C, Dahmen N. (2002): Venlafaxine in a patient with idiopathic leukopenia and mirtazapine-induced severe neutropenia. *J. Clin. Psychiatry* **63**, 838
32. Angst F, Stassen HH, Clayton PJ, Angst J. (2002a): Mortality of patients with mood disorders: follow-up over 34-38 years. *J Affect. Disord.* **68**, 167-181
33. Angst J, Angst F, Gerber-Werder R, Gamma A. (2005): Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. *Arch Suicide Res.* **9**, 279-300
34. Angst J, Angst K, Baruffol I, Meinherz-Surbeck R. (1992): ECT-Induced and Drug-Induced Hypomania. *Convuls. Ther.* **8**, 179-185
35. Angst J, Gamma A, Gastpar M, Lepine JP, Mendlewicz J, Tylee A. (2002b): Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. *Eur Arch. Psychiatry Clin. Neurosci.* **252**, 201-209
36. Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA. (2004): Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* **306**, 879-881
37. Anton SF and Revicki DA. (1995): The use of decision analysis in the pharmacoeconomic evaluation of an antidepressant: a cost-effectiveness study of nefazodone. *Psychopharmacol. Bull.* **31**, 249-258
38. Appelberg BG, Syvalahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. (2001): Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J. Clin. Psychiatry.* **62**, 448-452
39. Arinzon ZH, Lehman YA, Fidelman ZG, Krasnyansky II. (2002): Delayed recurrent SIADH associated with SSRIs. *Ann. Pharmacother.* **36**, 1175-1177
40. Aronson R, Offman HJ, Joffe RT, Naylor CD. (1996): Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Arch. Gen. Psychiatry.* **53**, 842-848
41. Artigas F, Adell A, Celada P. (2006): Pindolol augmentation of antidepressant response. *Curr. Drug Targets.* **7**, 139-147
42. Artigas F, Celada P, Laruelle M, Adell A. (2001): How does pindolol improve antidepressant action? *Trends Pharmacol. Sci.* **22**, 224-228

43. Avila A, Cardona X, Martin-Baranera M, Maho P, Sastre F, Bello J. (2003): Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial. *J. Clin. Psychopharmacol.* **23**, 509-513
44. Baboolal NS. (2004): Venlafaxine withdrawal syndrome: report of seven cases in Trinidad. *J. Clin. Psychopharmacol.* **24**, 229-231
45. Baca E, Garcia-Garcia M, Porras-Chavarino A. (2004): Gender differences in treatment response to sertraline versus imipramine in patients with nonmelancholic depressive disorders. *Prog. Neuropsychopharmacol. Biol Psychiatry.* **28**, 57-65
46. Baghai TC, Eser D, Schüle C, Nothdurfter C, Möller H-J, Rupprecht R. (2005): Elektrokonvulsionstherapie bei depressiven Störungen. *Journal für Neurologie, Neurochirurgie und Psychiatrie* **4/2005**, 20-28
47. Baghai TC, Möller H-J, Rupprecht R. (2006): Recent Progress in Pharmacological and Non-Pharmacological Treatment Options of Major Depression. *Current Pharmaceutical Design* **12**, 503-515
48. Baghai TC, Schule C, Zill P, Deiml T, Eser D, Zwanzger P, Ella R, Rupprecht R, Bondy B. (2004): The angiotensin I converting enzyme insertion/deletion polymorphism influences therapeutic outcome in major depressed women, but not in men. *Neurosci Lett.* **363**, 38-42
49. Baghai TC, Schule C, Zwanzger P, Zill P, Ella R, Eser D, Deiml T, Minov C, Rupprecht R, Bondy B. (2003): Influence of a functional polymorphism within the angiotensin I-converting enzyme gene on partial sleep deprivation in patients with major depression. *Neurosci Lett.* **339**, 223-226
50. Baldwin DS and Birtwistle J. (1998): The side effect burden associated with drug treatment of panic disorder. *J. Clin. Psychiatry* **59 Suppl 8**, 39-44
51. Baldwin DS, Montgomery SA, Nil R, Lader M. (2005a): Discontinuation symptoms in depression and anxiety disorders. *Int. J. Neuropsychopharmacol.* 1-12
52. Baldwin DS and Polkinghorn C. (2005b): Evidence-based pharmacotherapy of Generalized Anxiety Disorder. *Int. J. Neuropsychopharmacol.* **8**, 293-302
53. Baldwin RC, Anderson D, Black S, Evans S, Jones R, Wilson K, Iliffe S. (2003): Guideline for the management of late-life depression in primary care. *Int. J. Geriatr. Psychiatry* **18**, 829-838
54. Ballesteros J and Callado LF. (2004): Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. *J. Affect. Disord.* **79**, 137-147
55. Bano S, Akhter S, Afridi MI. (2004): Gender based response to fluoxetine hydrochloride medication in endogenous depression. *J Coll. Physicians Surg. Pak.* **14**, 161-165
56. Barbee JG, Conrad EJ, Jamhour NJ. (2004): The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. *J. Clin. Psychiatry* **65**, 975-981

57. Barbee JG and Jamhour NJ. (2002): Lamotrigine as an augmentation agent in treatment-resistant depression. *J. Clin. Psychiatry*. **63**, 737-741
58. Barbey JT and Roose SP. (1998): SSRI safety in overdose. *J Clin. Psychiatry* **59 Suppl 15**, 42-48
59. Barbosa L, Berk M, Vorster M. (2003): A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *J. Clin. Psychiatry*. **64**, 403-407
60. Barbour KA and Blumenthal JA. (2005): Exercise training and depression in older adults. *Neurobiol. Aging* **26 Suppl 1**, 119-123
61. Barden N, Reul JMHM, Holsboer F. (1995): Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? *Trends Neurosci.* **18**, 6-11
62. Barkin RL and Barkin S. (2005): The role of venlafaxine and duloxetine in the treatment of depression with decremental changes in somatic symptoms of pain, chronic pain, and the pharmacokinetics and clinical considerations of duloxetine pharmacotherapy. *Am. J. Ther.* **12**, 431-438
63. Barlow DH, Gorman JM, Shear MK, Woods SW. (2000): Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. *JAMA* **283**, 2529-2536
64. Bauer M, Adli M, Baethge C, Berghofer A, Sasse J, Heinz A, Bschor T. (2003): Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. *Can. J. Psychiatry* **48**, 440-448
65. Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Muller-Oerlinghausen B. (2000): Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *Am. J. Psychiatry*. **157**, 1429-1435
66. Bauer M and Döpfner S. (1999): Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J. Clin. Psychopharmacol.* **19**, 427-434
67. Bauer M, Hellweg R, Graf KJ, Baumgartner A. (1998): Treatment of refractory depression with high-dose thyroxine. *Neuropsychopharmacology* **18**, 444-455
68. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ. (2002a): World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. *World J. Biol. Psychiatry* **3**, 69-86
69. Bauer M, Whybrow PC, Angst J, Versiani M, Möller H-J, WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders. (2002b): World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of

- unipolar depressive disorder, Part 1: Acute and continuation treatment of major depressive disorder. *World J Biol Psychiatry* **3**, 4-43
70. Baumann P. (1996): Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin. Pharmacokinet.* **31**, 444-469
71. Baumann P and Eap CB. (2001): Enantiomeric antidepressant drugs should be considered on individual merit. *Hum. Psychopharmacol.* **16**, S85-S92
72. Baumann P, Ulrich S, Eckermann G, Gerlach M, Kuss HJ, Laux G, Muller-Oerlinghausen B, Rao ML, Riederer P, Zernig G, Hiemke C. (2005): The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants. *Dialogues. Clin. Neurosci.* **7**, 231-247
73. Baumann P, Zullino DF, Eap CB. (2002): Enantiomers' potential in psychopharmacology--a critical analysis with special emphasis on the antidepressant escitalopram. *Eur. Neuropsychopharmacol.* **12**, 433-444
74. Beck, A.T., Rush, A.J., Shaw, B.F. & Emery, G. (1979): *Cognitive Therapy of Depression*. Guilford, New York
75. Behnke K, Jensen GS, Graubaum HJ, Gruenwald J. (2002): Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. *Adv. Ther.* **19**, 43-52
76. Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF. (2001): Rapid reversal of psychotic depression using mifepristone. *J. Clin. Psychopharmacol.* **21**, 516-521
77. Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C, Schatzberg AF. (2002): An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol. Psychiatry* **52**, 386-392
78. Beliles K and Stoudemire A. (1998): Psychopharmacologic treatment of depression in the medically ill. *Psychosomatics* **39**, S2-19
79. Bell C, Abrams J, Nutt D. (2001): Tryptophan depletion and its implications for psychiatry. *Br. J Psychiatry*. **178:399-405**, 399-405
80. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. (1999): Ongoing lithium treatment prevents relapse after total sleep deprivation. *J. Clin. Psychopharmacol.* **19**, 240-245
81. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. (2001): Morning sunlight reduces length of hospitalization in bipolar depression. *J. Affect. Disord.* **62**, 221-223
82. Benedetti F, Colombo C, Pontiggia A, Bernasconi A, Florita M, Smeraldi E. (2003): Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J. Clin. Psychiatry* **64**, 648-653
83. Benkert O, Grunder G, Wetzel H, Hackett D. (1996): A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. *J Psychiatr. Res.* **30**, 441-451

84. Benkert O, Muller M, Szegedi A. (2002): An overview of the clinical efficacy of mirtazapine. *Hum. Psychopharmacol* **17 Suppl 1**, S23-S26
85. Benkert O, Szegedi A, Kohnen R. (2000): Mirtazapine compared with paroxetine in major depression. *J Clin. Psychiatry* **61**, 656-663
86. Bennett DS, Ambrosini PJ, Kudes D, Metz C, Rabinovich H. (2005): Gender differences in adolescent depression: do symptoms differ for boys and girls? *J Affect. Disord.* **89**, 35-44
87. Berard R, Fong R, Carpenter DJ, Thomason C, Wilkinson C. (2006): An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J. Child Adolesc. Psychopharmacol.* **16**, 59-75
88. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. (2000a): Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **47**, 351-354
89. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, Charney DS, Boutros NN. (2000b): A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol. Psychiatry* **47**, 332-337
90. Berndt ER, Finkelstein SN, Greenberg PE, Howland RH, Keith A, Rush AJ, Russell J, Keller MB. (1998): Workplace performance effects from chronic depression and its treatment. *J. Health Econ.* **17**, 511-535
91. Bielski RJ, Bose A, Chang CC. (2005): A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. *Ann. Clin. Psychiatry* **17**, 65-69
92. Birkenhager TK, Renes JW, Pluijms EM. (2004): One-year follow-up after successful ECT: a naturalistic study in depressed inpatients. *J. Clin. Psychiatry* **65**, 87-91
93. Birmaher B, Brent DA, Benson RS. (1998): Summary of the practice parameters for the assessment and treatment of children and adolescents with depressive disorders. American Academy of Child and Adolescent Psychiatry. *J. Am. Acad. Child Adolesc. Psychiatry* **37**, 1234-1238
94. Bitran D, Hilvers RJ, Kellogg CK. (1991): Anxiolytic effects of 3 α -hydroxy-5 α [β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABA_A receptor. *Brain Res.* **561**, 157-161
95. Bjerkenstedt L, Edman GV, Alken RG, Mannel M. (2005): Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. *Eur. Arch. Psychiatry Clin. Neurosci.* **255**, 40-47
96. Black DW, Winokur G, Nasrallah A. (1993): A Multivariate Analysis of the Experience of 423 Depressed Inpatients Treated with Electroconvulsive Therapy. *Convuls. Ther.* **9**, 112-120
97. Blakely RD. (2001): Physiological genomics of antidepressant targets: keeping the periphery in mind. *J. Neurosci.* **21**, 8319-8323

98. Blanco C, Raza MS, Schneier FR, Liebowitz MR. (2003): The evidence-based pharmacological treatment of social anxiety disorder. *Int. J. Neuropsychopharmacol.* **6**, 427-442
99. Blier P. (2001): Pharmacology of rapid-onset antidepressant treatment strategies. *J Clin. Psychiatry* **62 Suppl 15**, 12-17
100. Blier P. (2003): The pharmacology of putative early-onset antidepressant strategies. *Eur. Neuropsychopharmacol.* **13**, 57-66
101. Blier P and Ward NM. (2003): Is there a role for 5-HT_{1A} agonists in the treatment of depression? *Biol. Psychiatry.* **53**, 193-203
102. Bodkin JA and Amsterdam JD. (2002): Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. *Am. J. Psychiatry* **159**, 1869-1875
103. Boerner RJ and Möller HJ. (1999): The importance of new antidepressants in the treatment of anxiety/depressive disorders. *Pharmacopsychiatry* **32**, 119-126
104. Bogetto F, Bellino S, Revello RB, Patria L. (2002): Discontinuation syndrome in dysthymic patients treated with selective serotonin reuptake inhibitors: a clinical investigation. *CNS. Drugs* **16**, 273-283
105. Bolton P, Bass J, Neugebauer R, Verdelli H, Clougherty KF, Wickramaratne P, Speelman L, Ndogoni L, Weissman M. (2003): Group interpersonal psychotherapy for depression in rural Uganda: a randomized controlled trial. *JAMA* **289**, 3117-3124
106. Bolton P, Wilk CM, Ndogoni L. (2004): Assessment of depression prevalence in rural Uganda using symptom and function criteria. *Soc. Psychiatry Psychiatr. Epidemiol.* **39**, 442-447
107. Bondareff W, Alpert M, Friedhoff AJ, Richter EM, Clary CM, Batzar E. (2000): Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. *Am. J. Psychiatry* **157**, 729-736
108. Bonnet U. (2003): Moclobemide: therapeutic use and clinical studies. *CNS. Drug Rev.* **9**, 97-140
109. Borghi J and Guest JF. (2000): Economic impact of using mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in the UK. *Eur Psychiatry.* **15**, 378-387
110. Bosker FJ, Westerink BH, Cremers TI, Gerrits M, van der Hart MG, Kuipers SD, van der PG, ter Horst GJ, Den Boer JA, Korf J. (2004): Future antidepressants: what is in the pipeline and what is missing? *CNS. Drugs* **18**, 705-732
111. Bostic JQ, Rubin DH, Prince J, Schlozman S. (2005): Treatment of depression in children and adolescents. *J. Psychiatr. Pract.* **11**, 141-154
112. Bouali S, Evrard A, Chastanet M, Lesch KP, Hamon M, Adrien J. (2003): Sex hormone-dependent desensitization of 5-HT_{1A} autoreceptors in knockout mice deficient in the 5-HT transporter. *Eur J Neurosci.* **18**, 2203-2212

113. Bradvik L and Berglund M. (2005): Suicide in severe depression related to treatment: depressive characteristics and rate of antidepressant overdose. *Eur Arch Psychiatry Clin Neurosci.* **255**, 245-250
114. Brenner R, Azbel V, Madhusoodanan S, Pawlowska M. (2000): Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. *Clin. Ther.* **22**, 411-419
115. Breslau N, Schultz L, Peterson E. (1995): Sex differences in depression: a role for preexisting anxiety. *Psychiatry Res.* **58**, 1-12
116. Bridge JA, Salary CB, Birmaher B, Asare AG, Brent DA. (2005): The risks and benefits of antidepressant treatment for youth depression. *Ann. Med.* **37**, 404-412
117. Briley M. (1998): Specific serotonin and noradrenaline reuptake inhibitors (SNRIs). A review of their pharmacology, clinical efficacy and tolerability. *Human Psychopharmacology: Clinical and Experimental* **13**, 99-111
118. Brown C, Battista DR, Bruehlman R, Sereika SS, Thase ME, Dunbar-Jacob J. (2005): Beliefs about antidepressant medications in primary care patients: relationship to self-reported adherence. *Med Care.* **43**, 1203-1207
119. Brown CS and Bryant SG. (1988): Monoamine oxidase inhibitors: safety and efficacy issues. *Drug Intell. Clin. Pharm.* **22**, 232-235
120. Brown, G.W. & Harris, T. (1978): Social origins of depression: a study of psychiatric disorder in women. Tavistock Publications, London
121. Brown MC, Nimmerrichter AA, Guest JF. (1999): Cost-effectiveness of mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in Austria. *Eur Psychiatry.* **14**, 230-244
122. Browne G, Steiner M, Roberts J, Gafni A, Byrne C, Dunn E, Bell B, Mills M, Chalklin L, Wallik D, Kraemer J. (2002): Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs. *J. Affect. Disord.* **68**, 317-330
123. Bruck P, Antao CA, Henry JA. (1992): Generic prescribing of antidepressants. *J. R. Soc. Med.* **85**, 682-685
124. Brunello N, Mendlewicz J, Kasper S, Leonard B, Montgomery S, Nelson J, Paykel E, Versiani M, Racagni G. (2002): The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. *Eur. Neuropsychopharmacol.* **12**, 461-475
125. Bschor T, Berghofer A, Strohle A, Kunz D, Adli M, Muller-Oerlinghausen B, Bauer M. (2002): How long should the lithium augmentation strategy be maintained? A 1-year follow-up of a placebo-controlled study in unipolar refractory major depression. *J. Clin. Psychopharmacol.* **22**, 427-430
126. Burke, M.J. & Preskorn, S.H. (1995): Psychopharmacology: The fourth generation of progress. Bloom, F.E. & Kupfer, D.J. (eds.), pp. 1053-1065 (Raven Press, New York,

127. Burt T, Lisanby SH, Sackeim HA. (2002): Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int. J. Neuropsychopharmacol.* **5**, 73-103
128. Burt VK, Suri R, Altshuler L, Stowe Z, Hendrick VC, Muntean E. (2001): The use of psychotropic medications during breast-feeding. *Am. J. Psychiatry* **158**, 1001-1009
129. Campo-Arias A. (2004): [Antidepressants in migraine prophylaxis: an approximation]. *Rev. Neurol.* **38**, 864-868
130. Canadian Coordinating Office for Health Technology Assessment. (1997): Selective serotonin reuptake inhibitors (SSRI's) for major depression. Part II. The cost-effectiveness of SSRI's in treatment of depression. **Canadian Coordinating Office for Health Technology Assessment**, Ottawa
131. Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments (CANMAT). (2001): Clinical guidelines for the treatment of depressive disorders. *Can. J Psychiatry*. **46 Suppl 1:5S-90S**, 5S-90S
132. Carlsten A, Waern M, Ekedahl A, Ranstam J. (2001): Antidepressant medication and suicide in Sweden. *Pharmacoepidemiol. Drug Saf.* **10**, 525-530
133. Carrasco GA, Barker SA, Zhang Y, Damjanoska KJ, Sullivan NR, Garcia F, D'souza DN, Muma NA, van De Kar LD. (2004): Estrogen treatment increases the levels of regulator of G protein signaling-Z1 in the hypothalamic paraventricular nucleus: possible role in desensitization of 5-hydroxytryptamine1A receptors. *Neuroscience*. **127**, 261-267
134. Casciano J, Arikian S, Tarride JE, Doyle JJ, Casciano R. (1999): A pharmacoeconomic evaluation of major depressive disorder (Italy). *Epidemiol. Psychiatr. Soc.* **8**, 220-231
135. Casciano J, Doyle J, Arikian S, Casciano R. (2001): The health economic impact of antidepressant usage from a payer's perspective: a multinational study. *Int. J. Clin. Pract.* **55**, 292-299
136. Casciano R. (2003): Effectiveness measures of major depressive disorder in pharmacoeconomic evaluations. *Manag. Care Interface. Suppl B:14-5*, 14-15
137. Castren E. (2005): Is mood chemistry? *Nat. Rev. Neurosci.* **6**, 241-246
138. Chambers CD, Anderson PO, Thomas RG, Dick LM, Felix RJ, Johnson KA, Jones KL. (1999): Weight gain in infants breastfed by mothers who take fluoxetine. *Pediatrics* **104**, e61
139. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA. (2006): Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N. Engl. J. Med.* **354**, 579-587
140. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. (1996): Birth outcomes in pregnant women taking fluoxetine. *N. Engl. J. Med.* **335**, 1010-1015

141. Charney DS, Grothe DR, Smith SL, Brady KT, Katsounis-Puckett J, Wright CW, Laird LK, Rush AJ. (2002): Overview of psychiatric disorders and the role of newer antidepressants. *J. Clin. Psychiatry* **63**, 3-9
142. Cheeta S, Schifano F, Oyefeso A, Webb L, Ghodse AH. (2004): Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998-2000. *Br. J Psychiatry* **184**, 41-47
143. Chen F, Larsen MB, Sanchez C, Wiborg O. (2005): The S-enantiomer of R,S-citalopram, increases inhibitor binding to the human serotonin transporter by an allosteric mechanism. Comparison with other serotonin transporter inhibitors. *Eur. Neuropsychopharmacol.* **15**, 193-198
144. Cheng K, Yan H, Duan KJ. (2005): [Advances in clinical and mechanism studies of acupuncture and moxibustion for treatment of depression]. *Zhongguo Zhen. Jiu.* **25**, 221-223
145. Cheung AH, Emslie GJ, Mayes TL. (2005): Review of the efficacy and safety of antidepressants in youth depression. *J. Child Psychol. Psychiatry* **46**, 735-754
146. Chisholm D, Healey A, Knapp M. (1997): QALYs and mental health care. *Soc. Psychiatry Psychiatr. Epidemiol.* **32**, 68-75
147. Chiu HF. (1997): Antidepressants in the elderly. *Int. J. Clin. Pract.* **51**, 369-374
148. Cipriani A, Brambilla P, Furukawa T, Geddes J, Gregis M, Hotopf M, Malvini L, Barbui C. (2005): Fluoxetine versus other types of pharmacotherapy for depression. *Cochrane. Database. Syst. Rev.* **4**, CD004185
149. Ciusani E, Zullino DF, Eap CB, Brawand-Amey M, Brocard M, Baumann P. (2004): Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. *J. Psychopharmacol.* **18**, 559-566
150. Clayton AH, Zajecka J, Ferguson JM, Filipiak-Reisner JK, Brown MT, Schwartz GE. (2003): Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. *Int. Clin. Psychopharmacol.* **18**, 151-156
151. Cohen LS, Nonacs R, Viguera AC, Reminick A. (2004): Diagnosis and treatment of depression during pregnancy. *CNS. Spectr.* **9**, 209-216
152. Coleman CC, Cunningham LA, Foster VJ, Batey SR, Donahue RM, Houser TL, Ascher JA. (1999): Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann. Clin. Psychiatry* **11**, 205-215
153. Coleman CC, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N, Ascher J, Batey S, Jamerson B, Metz A. (2001): A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin. Ther.* **23**, 1040-1058

154. Collantes-Estevez E and Fernandez-Perez C. (2003): Improved control of osteoarthritis pain and self-reported health status in non-responders to celecoxib switched to rofecoxib: results of PAVIA, an open-label post-marketing survey in Spain. *Curr. Med. Res. Opin.* **19**, 402-410
155. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. (2000): Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res.* **95**, 43-53
156. Committee on Safety of Medicines. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. (2006)(24-1-2006). Ref Type: Internet Communication
157. Compton MT and Nemeroff CB. (2000): The treatment of bipolar depression. *J. Clin. Psychiatry* **61 Suppl 9**, 57-67
158. Compton SN, March JS, Brent D, Albano AM, Weersing R, Curry J. (2004): Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J. Am. Acad. Child Adolesc. Psychiatry* **43**, 930-959
159. Conway CR, McGuire JM, Baram VY. (2004): Nefazodone-induced liver failure. *J. Clin. Psychopharmacol.* **24**, 353-354
160. Coppen A. (2000): Lithium in unipolar depression and the prevention of suicide. *J. Clin. Psychiatry.* **61 Suppl 9:52-6.**, 52-56
161. Corruble E and Guelfi JD. (2000): Does increasing dose improve efficacy in patients with poor antidepressant response: a review. *Acta Psychiatr. Scand.* **101**, 343-348
162. Coryell W. (1996): Psychotic depression. *J. Clin. Psychiatry* **57 Suppl 3**, 27-31
163. Coryell W. (1998): The treatment of psychotic depression. *J. Clin. Psychiatry* **59 Suppl 1**, 22-27
164. Coryell W, Pfohl B, Zimmerman M. (1985): Outcome Following Electroconvulsive Therapy: A Comparison of Primary and Secondary Depression. *Convuls. Ther.* **1**, 10-14
165. Couturier JL. (2005): Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. *J. Psychiatry Neurosci.* **30**, 83-90
166. Craft LL and Perna FM. (2004): The Benefits of Exercise for the Clinically Depressed. *Prim. Care Companion. J. Clin. Psychiatry* **6**, 104-111
167. Croft H, Settle E Jr, Houser T, Batey SR, Donahue RM, Ascher JA. (1999): A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin. Ther.* **21**, 643-658
168. Cullen M, Mitchell P, Brodaty H, Boyce P, Parker G, Hickie I, Wilhelm K. (1991): Carbamazepine for treatment-resistant melancholia. *J. Clin. Psychiatry* **52**, 472-476

169. Culman J, Klee S, Ohlendorf C, Unger T. (1997): Effect of tachykinin receptor inhibition in the brain on cardiovascular and behavioral responses to stress. *J. Pharmacol. Exp. Ther.* **280**, 238-246
170. Cummings JL and Masterman DL. (1999): Depression in patients with Parkinson's disease. *Int. J. Geriatr. Psychiatry* **14**, 711-718
171. Cunningham LA, Borison RL, Carman JS, Chouinard G, Crowder JE, Diamond BI, Fischer DE, Hearst E. (1994): A comparison of venlafaxine, trazodone, and placebo in major depression. *J. Clin. Psychopharmacol.* **14**, 99-106
172. Curran S. (1995): Effect of paroxetine on seizure length during electroconvulsive therapy. *Acta Psychiatr. Scand.* **92**, 239-240
173. Curry JF. (2001): Specific psychotherapies for childhood and adolescent depression. *Biol. Psychiatry* **49**, 1091-1100
174. Cyr M and Brown CS. (1996): Nefazodone: its place among antidepressants. *Ann. Pharmacother.* **30**, 1006-1012
175. Czekalla J, Gastpar M, Hubner WD, Jager D. (1997): The effect of hypericum extract on cardiac conduction as seen in the electrocardiogram compared to that of imipramine. *Pharmacopsychiatry* **30 Suppl 2**, 86-88
176. Dam J, Ryde L, Svejso J, Lauge N, Lauritsen B, Bech P. (1998): Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. *Pharmacopsychiatry* **31**, 48-54
177. Dantzer R. (2004): Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. *Eur. J. Pharmacol.* **500**, 399-411
178. Darcourt G, Souetre E, Pringuey D, Robert P, Feuillade P, Belugou JL. (1992): [Disorders of circadian rhythms in depression]. *Encephale* **18 Spec No 4**, 473-478
179. Dardennes R, Berdeaux G, Lafuma A, Fagnani F. (1999): Comparison of the cost-effectiveness of milnacipran (a SNRI) with TCAs and SSRIs: a modeling approach. *Eur. Psychiatry* **14**, 152-162
180. Dardennes RM, Even C, Ballon N, Bange F. (1998): Serotonin syndrome caused by a clomipramine-moclobemide interaction. *J. Clin. Psychiatry* **59**, 382-383
181. Davidson J, McLeod M, Law-Yone B, Linnoila M. (1978): A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression. *Arch. Gen. Psychiatry* **35**, 639-642
182. Davidson J, Pearlstein T, Lonnberg P, Brady KT, Rothbaum B, Bell J, Maddock R, Hegel MT, Farfel G. (2001): Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am. J. Psychiatry* **158**, 1974-1981
183. Davidson J and Pelton S. (1986): Forms of atypical depression and their response to antidepressant drugs. *Psychiatry Res.* **17**, 87-95

184. Davidson JR, Connor KM, Hertzberg MA, Weisler RH, Wilson WH, Payne VM. (2005): Maintenance therapy with fluoxetine in posttraumatic stress disorder: a placebo-controlled discontinuation study. *J. Clin. Psychopharmacol.* **25**, 166-169
185. Davis LL, Kabel D, Patel D, Choate AD, Foslien-Nash C, Gurguis GN, Kramer GL, Petty F. (1996): Valproate as an antidepressant in major depressive disorder. *Psychopharmacol. Bull.* **32**, 647-652
186. Dawling S, Lynn K, Rosser R, Braithwaite R. (1982): Nortriptyline metabolism in chronic renal failure: metabolite elimination. *Clin. Pharmacol. Ther.* **32**, 322-329
187. Dawson LA and Nguyen HQ. (2000): The role of 5-HT(1A) and 5-HT(1B/1D) receptors on the modulation of acute fluoxetine-induced changes in extracellular 5-HT: the mechanism of action of (+/-)pindolol. *Neuropharmacology.* **39**, 1044-1052
188. de la Gandara J, Aguera L, Rojo JE, Ros S, de Pedro JM. (2005a): Use of antidepressant combinations: which, when and why? Results of a Spanish survey. *Acta Psychiatr. Scand. Suppl* 32-36
189. de la Gandara J, Rojo JE, Ros S, Aguera L, de Pedro JM. (2005b): Neuropharmacological basis of combining antidepressants. *Acta Psychiatr. Scand. Suppl* 11-3, 36
190. Defrance R, Marey C, Kamoun A. (1988): Antidepressant and anxiolytic activities of tianeptine: an overview of clinical trials. *Clin. Neuropharmacol.* **11 Suppl 2**, S74-S82
191. Degner D, Grohmann R, Kropp S, Ruther E, Bender S, Engel RR, Schmidt LG. (2004): Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. *Pharmacopsychiatry* **37 Suppl 1**, S39-S45
192. Delgado PL. (2004): How antidepressants help depression: mechanisms of action and clinical response. *J. Clin. Psychiatry* **65 Suppl 4**, 25-30
193. Deltito J and Beyer D. (1998): The scientific, quasi-scientific and popular literature on the use of St. John's Wort in the treatment of depression. *J. Affect. Disord.* **51**, 345-351
194. Demolis JL, Angebaud P, Grange JD, Coates P, Funck-Brentano C, Jaillon P. (1996): Influence of liver cirrhosis on sertraline pharmacokinetics. *Br. J. Clin. Pharmacol.* **42**, 394-397
195. Demyttenaere K. (1998): Noncompliance with antidepressants: who's to blame? *Int. Clin. Psychopharmacol.* **13 Suppl 2:S19-25.**, S19-S25
196. Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, de Girolamo G, Morosini P, Polidori G, Kikkawa T, Kawakami N, Ono Y, Takeshima T, Uda H, Karam EG, Fayyad JA, Karam AN, Mneimneh ZN, Medina-Mora ME, Borges G, Lara C, de Graaf R, Ormel J, Gureje O, Shen Y, Huang Y, Zhang M, Alonso J, Haro JM, Vilagut G, Bromet EJ, Gluzman S, Webb C, Kessler RC, Merikangas KR, Anthony JC, Von Korff MR, Wang PS, Brugha TS, Aguilar-Gaxiola S, Lee S, Heeringa S, Pennell BE, Zaslavsky AM, Ustun TB, Chatterji S. (2004): Prevalence, severity, and unmet need for treatment of mental

- disorders in the World Health Organization World Mental Health Surveys. *JAMA*. **291**, 2581-2590
197. Demyttenaere K, Hemels ME, Hudry J, Annemans L. (2005): A cost-effectiveness model of escitalopram, citalopram, and venlafaxine as first-line treatment for major depressive disorder in Belgium. *Clin. Ther.* **27**, 111-124
 198. Depression Guideline Panel. (1993): Clinical Practice Guideline. Depression in Primary Care. **Rockville, MD**,
 199. Derouesne C and Lacomblez L. (2004): [Depression and dementia]. *Psychol. Neuropsychiatr. Vieil.* **2 Suppl 1**, S35-S42
 200. Devanand DP, Sackeim HA, Prudic J. (1991): Electroconvulsive therapy in the treatment-resistant patient. *Psychiatr. Clin. North Am.* **14**, 905-923
 201. Dewa CS, Hoch JS, Lin E, Paterson M, Goering P. (2003): Pattern of antidepressant use and duration of depression-related absence from work. *Br. J. Psychiatry*. **183:507-13**, 507-513
 202. Dilsaver SC. (1988): Monoamine oxidase inhibitor withdrawal phenomena: symptoms and pathophysiology. *Acta Psychiatr. Scand.* **78**, 1-7
 203. Dingemans J, Kneer J, Fotteler B, Groen H, Peeters PA, Jonkman JH. (1995): Switch in treatment from tricyclic antidepressants to moclobemide: a new generation monoamine oxidase inhibitor. *J. Clin. Psychopharmacol.* **15**, 41-48
 204. Dingemans J, Wallnofer A, Gieschke R, Guentert T, Amrein R. (1998): Pharmacokinetic and pharmacodynamic interactions between fluoxetine and moclobemide in the investigation of development of the "serotonin syndrome". *Clin. Pharmacol. Ther.* **63**, 403-413
 205. Dodd S, Horgan D, Malhi GS, Berk M. (2005): To combine or not to combine? A literature review of antidepressant combination therapy. *J. Affect. Disord.* **89**, 1-11
 206. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L. (2002): Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar. Disord.* **4 Suppl 1**, 94-95
 207. Doyle JJ, Casciano J, Arikian S, Tarride JE, Gonzalez MA, Casciano R. (2001): A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. *Value. Health.* **4**, 16-31
 208. Drummond, M. & McGuire, A. (2001): Economic evaluation in health care: merging theory with practice. Oxford University Press, Oxford
 209. Drummond, M., Sculpher, M.J., Torrance, G.W., O'Brien, B.J. & Stoddart, G.L. (2005): Methods for the economic evaluation of health care programmes. Oxford University Press, Oxford
 210. Duggal HS, Gates C, Pathak PC. (2004): Olanzapine-induced neutropenia: mechanism and treatment. *J. Clin. Psychopharmacol.* **24**, 234-235

211. Duman RS and Monteggia LM. (2006): A Neurotrophic Model for Stress-Related Mood Disorders. *Biol. Psychiatry*
212. Dunner DL. (1998): Lithium carbonate: maintenance studies and consequences of withdrawal. *J. Clin. Psychiatry*. **59 Suppl 6:48-55; discussion 56.**, 48-55
213. Dunningham W, de Aguiar WM, de Lourdes Costa Pinto M. (1994): A double-blind Brazilian study of efficacy and safety of moclobemide versus imipramine in the treatment of patients with geriatric depression. *Aquivos Brasileiros de Medicina* **68**, 402-405
214. Eaton WW. (2002): Epidemiologic evidence on the comorbidity of depression and diabetes. *J. Psychosom. Res.* **53**, 903-906
215. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. (1996): Depression and risk for onset of type II diabetes. A prospective population-based study. *Diabetes Care* **19**, 1097-1102
216. Ebmeier KP, Donaghey C, Steele JD. (2006): Recent developments and current controversies in depression. *Lancet* **367**, 153-167
217. ECT review group. (2003): Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* **361**, 799-808
218. Edwards JG and Anderson I. (1999): Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* **57**, 507-533
219. Einarson TR, Addis A, Iskedjian M. (1997): Pharmacoeconomic analysis of venlafaxine in the treatment of major depressive disorder. *Pharmacoeconomics*. **12**, 286-296
220. Einarson TR, Arikian S, Sweeney S, Doyle J. (1995): A model to evaluate the cost-effectiveness of oral therapies in the management of patients with major depressive disorders. *Clin. Ther.* **17**, 136-153
221. Einarson TR and Einarson A. (2005): Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. *Pharmacoepidemiol. Drug Saf* **14**, 823-827
222. Eker SS, Akkaya C, Akgoz S, Sarandol A, Kirli S. (2005): [Comparison of reboxetine and sertraline in terms of efficacy and safety in major depressive disorder]. *Turk. Psikiyatri. Derg.* **16**, 153-163
223. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, . (1989a): National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch. Gen. Psychiatry* **46**, 971-982
224. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, . (1989b): National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch. Gen. Psychiatry* **46**, 971-982

225. Ellingrod VL and Perry PJ. (1995): Nefazodone: a new antidepressant. *Am. J. Health Syst. Pharm.* **52**, 2799-2812
226. Emslie GJ, Heiligenstein JH, Hoog SL, Wagner KD, Findling RL, McCracken JT, Nilsson ME, Jacobson JG. (2004): Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J. Am. Acad. Child Adolesc. Psychiatry* **43**, 1397-1405
227. Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. (2002): Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J. Am. Acad. Child Adolesc. Psychiatry* **41**, 1205-1215
228. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. (1997): A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch. Gen. Psychiatry* **54**, 1031-1037
229. Emslie GJ, Ryan ND, Wagner KD. (2005): Major depressive disorder in children and adolescents: clinical trial design and antidepressant efficacy. *J. Clin. Psychiatry* **66 Suppl 7**, 14-20
230. Emslie,GJ, Wagner,KD, Kutcher,S, Krulewicz,S, Fong,R, Carpenter,DJ, Lipschitz,A, Machin,A & Wilkinson,C. Paroxetine Treatment in Children and Adolescents with Major Depressive Disorder: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial. (2006)*J. Am. Acad. Child Adolesc. Psychiatry* . Ref Type: In Press
231. Ernst CL and Goldberg JF. (2002): The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. *J. Clin. Psychiatry* **63 Suppl 4**, 42-55
232. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, DeLong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P, Jr., Valvo WJ. (2005): Mood disorders in the medically ill: scientific review and recommendations. *Biol. Psychiatry* **58**, 175-189
233. Fava GA. (2003a): Can long-term treatment with antidepressant drugs worsen the course of depression? *J. Clin. Psychiatry* **64**, 123-133
234. Fava M. (2002): Somatic symptoms, depression, and antidepressant treatment. *J. Clin. Psychiatry* **63**, 305-307
235. Fava M. (2003b): The role of the serotonergic and noradrenergic neurotransmitter systems in the treatment of psychological and physical symptoms of depression. *J. Clin. Psychiatry* **64 Suppl 13**, 26-29

236. Fava M, Alpert J, Nierenberg AA, Mischoulon D, Otto MW, Zajecka J, Murck H, Rosenbaum JF. (2005a): A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *J. Clin. Psychopharmacol.* **25**, 441-447
237. Fava M, Mulroy R, Alpert J, Nierenberg AA, Rosenbaum JF. (1997): Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *Am. J. Psychiatry* **154**, 1760-1762
238. Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, Kupfer DJ. (2003): Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. *Psychiatr. Clin. North Am.* **26**, 457-94, x
239. Fava M, Thase ME, DeBattista C. (2005b): A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin. Psychiatry.* **66**, 85-93
240. Feiger AD. (1996): A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of outpatient major depression. *Psychopharmacol. Bull.* **32**, 659-665
241. Feiger AD, Heiser JF, Shrivastava RK, Weiss KJ, Smith WT, Sitsen JM, Gibertini M. (2003): Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. *J. Clin. Psychiatry* **64**, 243-249
242. Feighner J, Hendrickson G, Miller L, Stern W. (1986): Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J. Clin. Psychopharmacol.* **6**, 27-32
243. Feighner JP, Gardner EA, Johnston JA, Batey SR, Khayrallah MA, Ascher JA, Lineberry CG. (1991): Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J. Clin. Psychiatry* **52**, 329-335
244. Feighner JP, Herbstein J, Damlouji N. (1985): Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. *J. Clin. Psychiatry* **46**, 206-209
245. Ferguson JM. (2001): SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Prim. Care Companion. J Clin. Psychiatry* **3**, 22-27
246. Fernandez JL, Montgomery S, Francois C. (2005): Evaluation of the cost effectiveness of escitalopram versus venlafaxine XR in major depressive disorder. *Pharmacoeconomics.* **23**, 155-167
247. Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ. (2001): Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. *Acta Psychiatr. Scand.* **103**, 66-72
248. Fineberg NA and Gale TM. (2005): Evidence-based pharmacotherapy of obsessive-compulsive disorder. *Int. J. Neuropsychopharmacol.* **8**, 107-129
249. Finfgeld DL. (2003): SSRI-related hyponatremia among aging adults. *J Psychosoc. Nurs. Ment. Health Serv.* **41**, 12-16

250. Fink M. (1990): Is Catatonia a Primary Indication for ECT? *Convuls. Ther.* **6**, 1-4
251. Fink M. (1992): Catatonia and DSM-IV. *Convuls. Ther.* **8**, 159-162
252. Fink,M. (1999): *Electroshok: Restoring the mind*. Oxford University Press, New York
253. Fink M, Abrams R, Bailine S, Jaffe R. (1996a): Ambulatory electroconvulsive therapy: report of a task force of the association for convulsive therapy. Association for Convulsive Therapy. *Convuls. Ther.* **12**, 42-55
254. Fink M and Sackeim HA. (1996b): Convulsive therapy in schizophrenia? *Schizophr. Bull.* **22**, 27-39
255. Fink,M. & Taylor,M.A. (2003): *Catatonia. A clinician's guide to diagnosis and treatment*. Cambridge University Press, Cambridge
256. Finkelstein FO, Watnick S, Finkelstein SH, Wuerth D. (2002): The treatment of depression in patients maintained on dialysis. *J. Psychosom. Res.* **53**, 957-960
257. Folkerts HW, Michael N, Tolle R, Schonauer K, Mucke S, Schulze-Monking H. (1997): Electroconvulsive therapy vs. paroxetine in treatment-resistant depression -- a randomized study. *Acta Psychiatr. Scand.* **96**, 334-342
258. Forder J, Kavanagh S, Fenyo A. (1996): A comparison of the cost-effectiveness of sertraline versus tricyclic antidepressants in primary care. *J. Affect. Disord.* **38**, 97-111
259. Foulkes NS, Borjigin J, Snyder SH, Sassone-Corsi P. (1997): Rhythmic transcription: the molecular basis of circadian melatonin synthesis. *Trends Neurosci.* **20**, 487-492
260. Fountoulakis,KN, Vieta,E, Bouras,C, Notaridis,G, Giannakopoulos,P, Kaprinis,G & Akiskal,HS. Lithium toxicity. A systematic review of existing data. (2006). Ref Type: Unpublished Work
261. Franchini L, Gasperini M, Perez J, Smeraldi E, Zanardi R. (1998): Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. *J Clin Psychiatry.* **59**, 229-232
262. Franco-Bronson K. (1996): The management of treatment-resistant depression in the medically ill. *Psychiatr. Clin. North Am.* **19**, 329-350
263. Francois C, Sinronen H, Toumi M. (2002): Introduction of escitalopram, a new SSRI in Finland: comparison of cost-effectiveness between the other SSRs and SNRI for the treatment of depression and estimation of the budgetary impact. *J. Medical Economics* **5**, 91-107
264. Francois C, Toumi M, Aakhus AM, Hansen K. (2003): A pharmacoeconomic evaluation of escitalopram, a new selective serotonin reuptake inhibitor. Comparison of cost-effectiveness between escitalopram, citalopram, fluoxetine, and venlafaxine for the treatment of depression in Norway. *Eur J. Health Econ.* **4**, 12-19
265. Frank E, Carpenter LL, Kupfer DJ. (1988): Sex differences in recurrent depression: are there any that are significant? *Am. J Psychiatry.* **145**, 41-45

266. Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ. (1990): Three-year outcomes for maintenance therapies in recurrent depression. *Arch. Gen. Psychiatry*. **47**, 1093-1099
267. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. (2005): Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch. Gen. Psychiatry* **62**, 996-1004
268. Frasere-Smith N, Lesperance F, Julien P. (2004): Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol. Psychiatry* **55**, 891-896
269. Frasere-Smith N, Lesperance F, Talajic M. (1993): Depression following myocardial infarction. Impact on 6-month survival. *JAMA* **270**, 1819-1825
270. Frazer A. (2001): Serotonergic and noradrenergic reuptake inhibitors: prediction of clinical effects from in vitro potencies. *J. Clin. Psychiatry* **62**, 16-23
271. Freeman H, Arikian S, Lenox-Smith A. (2000): Pharmacoeconomic analysis of antidepressants for major depressive disorder in the United Kingdom. *Pharmacoeconomics*. **18**, 143-148
272. Freeman MP, Hibbeln JR, Wisner KL, Brumbach BH, Watchman M, Gelenberg AJ. (2006): Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatr. Scand.* **113**, 31-35
273. Frey R, Schreinzer D, Heiden A, Kasper S. (2001): [Use of electroconvulsive therapy in psychiatry]. *Nervenarzt* **72**, 661-676
274. Frey R, Schreinzer D, Stimpfl T, Vycudilik W, Berzlanovich A, Kasper S. (2002): [Fatal poisonings with antidepressive drugs and neuroleptics. Analysis of a correlation with prescriptions in Vienna 1991 to 1997]. *Nervenarzt* **73**, 629-636
275. Furlong RA, Ho L, Rubinsztein JS, Walsh C, Paykel ES, Rubinsztein DC. (1999): Analysis of the monoamine oxidase A (MAOA) gene in bipolar affective disorder by association studies, meta-analyses, and sequencing of the promoter. *Am. J. Med. Genet.* **88**, 398-406
276. Furukawa T, McGuire H, Barbui C. (2003): Low dosage tricyclic antidepressants for depression. *Cochrane. Database. Syst. Rev.* CD003197
277. Furukawa T, Streiner DL, Young LT. (2000): Antidepressant plus benzodiazepine for major depression. *Cochrane. Database. Syst. Rev.* CD001026
278. Furukawa TA, Streiner DL, Young LT. (2001): Is antidepressant-benzodiazepine combination therapy clinically more useful? A meta-analytic study. *J. Affect. Disord.* **65**, 173-177
279. Gallagher,P & Young,AH. Mifepristone (RU-486) treatment for depression and psychosis: a review of the therapeutic implications. (2006)*Neuropsychiatric Disease and Treatment*
. Ref Type: In Press

280. Gallagher SM, Allen JJ, Hitt SK, Schnyer RN, Manber R. (2001): Six-month depression relapse rates among women treated with acupuncture. *Complement Ther. Med.* **9**, 216-218
281. Gallinat J, Boetsch T, Padberg F, Hampel H, Herrmann WM, Hegerl U. (2000): Is the EEG helpful in diagnosing and monitoring lithium intoxication? A case report and review of the literature. *Pharmacopsychiatry* **33**, 169-173
282. Gangadhar BN, Kapur RL, Kalyanasundaram S. (1982): Comparison of electroconvulsive therapy with imipramine in endogenous depression: a double blind study. *Br. J. Psychiatry* **141**, 367-371
283. Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, Mico J, Lafau O, Lafuente L. (2001a): Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *J. Affect. Disord.* **64**, 271-275
284. Garcia-Toro M, Pascual-Leone A, Romera M, Gonzalez A, Mico J, Ibarra O, Arnillas H, Capllonch I, Mayol A, Tormos JM. (2001b): Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. *J. Neurol. Neurosurg. Psychiatry.* **71**, 546-548
285. Gardner DM and Lynd LD. (1998): Sumatriptan contraindications and the serotonin syndrome. *Ann. Pharmacother.* **32**, 33-38
286. Gareri P, Stilo G, Bevacqua I, Mattace R, Ferreri G, De Sarro G. (1998): Antidepressant drugs in the elderly. *Gen. Pharmacol.* **30**, 465-475
287. Garner EM, Kelly MW, Thompson DF. (1993): Tricyclic antidepressant withdrawal syndrome. *Ann. Pharmacother.* **27**, 1068-1072
288. Gastpar M, Singer A, Zeller K. (2005): Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. *Pharmacopsychiatry* **38**, 78-86
289. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. (2003): Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* **361**, 653-661
290. Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J. (2000): SSRIs versus other antidepressants for depressive disorder. *Cochrane. Database. Syst. Rev.* CD001851
291. Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, Williams DA, Mease PJ, McLean SA, Clauw DJ. (2005): Efficacy of milnacipran in patients with fibromyalgia. *J. Rheumatol.* **32**, 1975-1985
292. Gentile S. (2005): The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf* **28**, 137-152
293. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, Howland R, Kling MA, Moreno F, Rittberg B, Dunner D, Schwartz T, Carpenter L, Burke M, Ninan P, Goodnick P. (2005): A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol. Psychiatry* **58**, 364-373

294. George MS, Rush AJ, Sackeim HA, Marangell LB. (2003): Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders. *Int. J. Neuropsychopharmacol* **6**, 73-83
295. Gerson S, Belin TR, Kaufman A, Mintz J, Jarvik L. (1999): Pharmacological and psychological treatments for depressed older patients: a meta-analysis and overview of recent findings. *Harv. Rev. Psychiatry* **7**, 1-28
296. Ghadirian AM, Engelsmann F, Dhar V, Filipini D, Keller R, Chouinard G, Murphy BEP. (1995): The psychotropic effects of inhibitors of steroid biosynthesis in depressed patients refractory to treatment. *Biol. Psychiatry* **37**, 369-375
297. Ghaziuddin N, Laughrin D, Giordani B. (2000): Cognitive side effects of electroconvulsive therapy in adolescents. *J. Child Adolesc. Psychopharmacol.* **10**, 269-276
298. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. (2005): The relationship between antidepressant medication use and rate of suicide. *Arch. Gen. Psychiatry* **62**, 165-172
299. Gibson AC. (1974): Letter: Agranulocytosis after treatment with clomipramine infusion. *Br. J. Psychiatry* **125**, 111-112
300. Goldberg JF. (2003): When do antidepressants worsen the course of bipolar disorder? *J. Psychiatr. Pract.* **9**, 181-194
301. Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T, Wisner KL, Nemeroff CB. (2005): The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am. J. Psychiatry* **162**, 656-662
302. Goldstein BJ and Goodnick PJ. (1998): Selective serotonin reuptake inhibitors in the treatment of affective disorders--III. Tolerability, safety and pharmacoeconomics. *J Psychopharmacol* **12**, S55-S87
303. Goodwin GM. (2003): Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol.* **17**, 149-173
304. Gould TD and Manji HK. (2004): The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. *J. Clin. Psychiatry* **65**, 598-604
305. Gravenor DS, Leclerc JR, Blake G. (1986): Tricyclic antidepressant agranulocytosis. *Can. J. Psychiatry* **31**, 661
306. Greenberg L and Fink M. (1992): The use of electroconvulsive therapy in geriatric patients. *Clin. Geriatr. Med.* **8**, 349-354
307. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. (2003): The economic burden of depression in the United States: how did it change between 1990 and 2000? *J. Clin. Psychiatry.* **64**, 1465-1475
308. Greenblatt M, Grosser GH, Wechsler HA. (1964): Differential response of hospitalized depressed patients in somatic therapy. *Am. J. Psychiatry* 935-943

309. Grigoriadis S, Kennedy SH, Srinivisan J, McIntyre RS, Fulton K. (2005): Antidepressant augmentation with raloxifene. *J Clin. Psychopharmacol.* **25**, 96-98
310. Grogan R, Wagner DR, Sullivan T, Labar D. (1995): Generalized nonconvulsive status epilepticus after electroconvulsive therapy. *Convuls. Ther.* **11**, 51-56
311. Grote NK and Frank E. (2003): Difficult-to-treat depression: the role of contexts and comorbidities. *Biol. Psychiatry* **53**, 660-670
312. Grube M and Hartwich P. (1990): Maintenance of antidepressant effect of sleep deprivation with the help of lithium. *Eur. Arch. Psychiatry Clin. Neurosci.* **240**, 60-61
313. Grundemar L and Hakanson R. (1994): Neuropeptide Y effector systems: perspectives for drug development. *Trends Pharmacol. Sci.* **15**, 153-159
314. Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, Lefkifker E. (2000): Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol. Psychiatry* **47**, 314-324
315. Grunhaus L, Pande AC, Brown MB, Greden JF. (1994): Clinical characteristics of patients with concurrent major depressive disorder and panic disorder. *Am. J. Psychiatry* **151**, 541-546
316. Grunhaus L, Rabin D, Greden JF. (1986): Simultaneous panic and depressive disorder: response to antidepressant treatments. *J. Clin. Psychiatry* **47**, 4-7
317. Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. (2003): A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol. Psychiatry* **53**, 324-331
318. Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, Vieta E, Moller HJ. (2002): World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: Treatment of bipolar depression. *World J. Biol. Psychiatry* **3**, 115-124
319. Guma M, Clemente F, Segura A, Costa J. (1999): [The serotonergic syndrome: moclobemide and citalopram]. *Med. Clin. (Barc.)* **113**, 677-678
320. Gureje,O, Lasebikan,VO, Kola,L & Makanjuola,VA. Lifetime and 12-month prevalence of mental disorders in the Nigerian Survey of Mental Health and Wellbeing. (2006)British Journal of Psychiatry . Ref Type: In Press
321. Hackett ML, Anderson CS, House AO. (2004): Interventions for treating depression after stroke. *Cochrane. Database. Syst. Rev.* CD003437
322. Haddad P. (1998): The SSRI discontinuation syndrome. *J. Psychopharmacol.* **12**, 305-313
323. Haddad P. (1999): Do antidepressants have any potential to cause addiction? *J. Psychopharmacol.* **13**, 300-307

324. Haddad PM. (2001): Antidepressant discontinuation syndromes. *Drug Saf.* **24**, 183-197
325. Hager ED, Dziambor H, Winkler P, Hohmann D, Macholdt K. (2002): Effects of lithium carbonate on hematopoietic cells in patients with persistent neutropenia following chemotherapy or radiotherapy. *J. Trace Elem. Med. Biol.* **16**, 91-97
326. Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. (2003): Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ* **326**, 1008
327. Hamalainen J, Isometsa E, Laukkala T, Kaprio J, Poikolainen K, Heikkinen M, Lindeman S, Aro H. (2004): Use of health services for major depressive episode in Finland. *J. Affect. Disord.* **79**, 105-112
328. Hameed U, Schwartz TL, Malhotra K, West RL, Bertone F. (2005): Antidepressant treatment in the primary care office: outcomes for adjustment disorder versus major depression. *Ann. Clin. Psychiatry* **17**, 77-81
329. Hamilton, J.A., Grant, M. & Jensvold, M.F. (1995): Psychopharmacology of Women: Sex, Gender and Hormonal Considerations. Jensvold, M.F., Halbreich, U. & Hamilton, J.A. (eds.) (American Psychiatric Press, Washington DC,
330. Hamilton M. (1967): Development of a rating scale for primary depressive illness. *Br. J Soc. Clin. Psychol.* **6**, 278-296
331. Hamilton M. (1986): The Hamilton rating scale for depression. In: Sartorius N., Ban, T. A. (Ed.) *Assessment of Depression*. Springer, Berlin, pp. 143-152
332. Hammad, T.A. Relationship between psychotropic drugs and pediatric suicidality. (2006)(24-1-2006).
Ref Type: Internet Communication
333. Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS. (2005): Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. *Ann. Intern. Med.* **143**, 415-426
334. Hantz P, Caradoc-Davies G, Caradoc-Davies T, Weatherall M, Dixon G. (1994): Depression in Parkinson's disease. *Am. J Psychiatry* **151**, 1010-1014
335. Harris EC and Barraclough B. (1998): Excess mortality of mental disorder. *Br. J Psychiatry.* **173:11-53.**, 11-53
336. Harvey BH, McEwen BS, Stein DJ. (2003): Neurobiology of antidepressant withdrawal: implications for the longitudinal outcome of depression. *Biol Psychiatry.* **54**, 1105-1117
337. Hasin DS, Goodwin RD, Stinson FS, Grant BF. (2005): Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch. Gen. Psychiatry* **62**, 1097-1106
338. Hasler G, Drevets WC, Manji HK, Charney DS. (2004): Discovering endophenotypes for major depression. *Neuropsychopharmacology* **29**, 1765-1781

339. Hatziaandreu EJ, Brown RE, Revicki DA, Turner R, Martindale J, Levine S, Siegel JE. (1994): Cost utility of maintenance treatment of recurrent depression with sertraline versus episodic treatment with dothiepin. *Pharmacoeconomics*. **5**, 249-268
340. Hatzinger M, Hemmeter UM, Baumann K, Brand S, Holsboer-Trachsler E. (2002): The combined DEX-CRH test in treatment course and long-term outcome of major depression. *J Psychiatr. Res.* **36**, 287-297
341. Hazell P, O'Connell D, Heathcote D, Henry D. (2002): Tricyclic drugs for depression in children and adolescents. *Cochrane. Database. Syst. Rev.* CD002317
342. Healy D and Whitaker C. (2003): Antidepressants and suicide: risk-benefit conundrums. *J. Psychiatry Neurosci.* **28**, 331-337
343. Hegerl,U, Althaus,D, Schmidtke,A & Niklewski,G. The Alliance against Depression: Two Year Evaluation of a Community Based Intervention to Reduce Suicidality. (2006)Psychol. Med.
Ref Type: In Press
344. Helgason T, Tomasson H, Zoega T. (2004): Antidepressants and public health in Iceland. Time series analysis of national data. *Br. J. Psychiatry* **184**, 157-162
345. Hemels ME, Kasper S, Walter E, Einarson TR. (2004a): Cost-effectiveness analysis of escitalopram: a new SSRI in the first-line treatment of major depressive disorder in Austria. *Curr. Med. Res. Opin.* **20**, 869-878
346. Hemels ME, Kasper S, Walter E, Einarson TR. (2004b): Cost-effectiveness of escitalopram versus citalopram in the treatment of severe depression. *Ann. Pharmacother.* **38**, 954-960
347. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. (2002): St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br. J. Clin. Pharmacol.* **54**, 349-356
348. Henkel V, Mergl R, Allgaier AK, Kohnen R, Möller HJ, Hegerl U. (2006): Treatment of depression with atypical features: a meta-analytic approach. *Psychiatry Res.* **141**, 89-101
349. Hennessy M, Kelleher D, Spiers JP, Barry M, Kavanagh P, Back D, Mulcahy F, Feely J. (2002): St Johns wort increases expression of P-glycoprotein: implications for drug interactions. *Br. J. Clin. Pharmacol.* **53**, 75-82
350. Henriksson S, Boethius G, Isacson G. (2001): Suicides are seldom prescribed antidepressants: findings from a prospective prescription database in Jamtland county, Sweden, 1985-95. *Acta Psychiatr. Scand.* **103**, 301-306
351. Heuser I, Deuschle M, Luppä P, Schweiger U, Standhardt H, Weber B. (1998): Increased diurnal plasma concentrations of dehydroepiandrosterone in depressed patients. *J. Clin. Endocrinol. Metab.* **83**, 3130-3133
352. Hibbeln JR. (1998): Fish consumption and major depression. *Lancet* **351**, 1213

- 353. Hickie I, Scott E, Naismith S, Ward PB, Turner K, Parker G, Mitchell P, Wilhelm K. (2001): Late-onset depression: genetic, vascular and clinical contributions. *Psychol. Med.* **31**, 1403-1412
- 354. Hildebrandt MG, Steyerberg EW, Stage KB, Passchier J, Kragh-Soerensen P. (2003): Are gender differences important for the clinical effects of antidepressants? *Am. J. Psychiatry*. **160**, 1643-1650
- 355. Hill GE, Wong KC, Hodges MR. (1976): Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. *Anesthesiology* **44**, 439-442
- 356. Hill GE, Wong KC, Hodges MR. (1977): Lithium carbonate and neuromuscular blocking agents. *Anesthesiology* **46**, 122-126
- 357. Himmelhoch JM, Thase ME, Mallinger AG, Houck P. (1991): Tranylcypromine versus imipramine in anergic bipolar depression. *Am. J. Psychiatry* **148**, 910-916
- 358. Hirschfeld RM. (2000): Antidepressants in long-term therapy: a review of tricyclic antidepressants and selective serotonin reuptake inhibitors. *Acta Psychiatr. Scand. Suppl.* **403:35-8.**, 35-38
- 359. Hirschfeld RM. (2001): Clinical importance of long-term antidepressant treatment. *Br. J. Psychiatry Suppl.* **42:S4-8.**, S4-S8
- 360. Hirschfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M, Hawley C, Kasper S, Linden M, Massana J, Mendlewicz J, Moller HJ, Nemeroff CB, Saiz J, Such P, Torta R, Versiani M. (2002): Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. *J. Clin. Psychiatry* **63**, 826-837
- 361. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, Lovett ML, Young PR, Haman KL, Freeman BB, Gallop R. (2005a): Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch. Gen. Psychiatry* **62**, 417-422
- 362. Hollon SD, Jarrett RB, Nierenberg AA, Thase ME, Trivedi M, Rush AJ. (2005c): Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? *J. Clin. Psychiatry* **66**, 455-468
- 363. Hollon SD, Jarrett RB, Nierenberg AA, Thase ME, Trivedi M, Rush AJ. (2005b): Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? *J. Clin. Psychiatry* **66**, 455-468
- 364. Hollon SD, Thase ME, Markowitz JC. (2002): Treatment and Prevention of Depression. *Psychological Science in the Public Interest* **3**, 39-77
- 365. Holsboer F. (2001): Antidepressant drug discovery in the postgenomic era. *World J. Biol. Psychiatry* **2**, 165-177
- 366. Holsboer F and Barden N. (1996): Antidepressants and hypothalamic-pituitary-adrenocortical regulation. *Endocr. Rev.* **17**, 187-205

367. Hosak L, Tuma I, Hanus H, Straka L. (2000): Costs and outcomes of use of amitriptyline, citalopram and fluoxetine in major depression: exploratory study. *Acta Medica. (Hradec. Kralove)*. **43**, 133-137
368. Howard P and Knight C. (2004): A clinical and cost-effectiveness comparison of venlafaxine and selective serotonin reuptake inhibitors (SSRIs) in the management of patients with major depressive disorders from the perspective of an Austrian sickness fund. *J. Medical Economics* **7**, 93-106
369. Hu TW. (2004): The economic burden of depression and reimbursement policy in the Asia Pacific region. *Australas. Psychiatry*. **12 Suppl:S11-5.**, S11-S15
370. Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, Biggs MM, O'Connor K, Rasmussen K, Little M, Zhao W, Bernstein HJ, Smith G, Mueller M, McClintock SM, Bailine SH, Kellner CH. (2004): Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. *J. Clin Psychiatry* **65**, 485-491
371. Imbarlina MJ, Sarkar S, Marwah S, Parepally H, Johnston PR, Brar JS, Chengappa KN. (2004): Leukopenia in clozapine treated patients may be induced by other drugs: a case series. *Eur. Psychiatry* **19**, 506-509
372. Inskip HM, Harris EC, Barraclough B. (1998): Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. *Br. J Psychiatry*. **172:35-7.**, 35-37
373. Isacson G, Holmgren P, Ahlner J. (2005a): Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. *Acta Psychiatr. Scand.* **111**, 286-290
374. Isacson G, Holmgren P, Druid H, Bergman U. (1997): The utilization of antidepressants--a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992-1994. *Acta Psychiatr. Scand.* **96**, 94-100
375. Isacson G and Rich CL. (2005b): Antidepressant drug use and suicide prevention. *Int Rev. Psychiatry*. **17**, 153-162
376. Isbister GK, Dawson A, Whyte IM, Prior FH, Clancy C, Smith AJ. (2001): Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? *Arch. Dis. Child Fetal Neonatal Ed* **85**, F147-F148
377. Izzo AA and Ernst E. (2001): Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* **61**, 2163-2175
378. Jacobson NS, Dobson KS, Truax PA, Addis ME, Koerner K, Gollan JK, Gortner E, Prince SE. (1996): A component analysis of cognitive-behavioral treatment for depression. *J Consult Clin. Psychol.* **64**, 295-304
379. Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. (2004): Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Arch. Gen. Psychiatry* **61**, 1235-1244
380. Janicak PG, Davis JM, Gibbons RD, Ericksen S, Chang S, Gallagher P. (1985): Efficacy of ECT: a meta-analysis. *Am. J. Psychiatry* **142**, 297-302

381. Jansson M, Gatz M, Berg S, Johansson B, Malmberg B, McClearn GE, Schalling M, Pedersen NL. (2004): Gender differences in heritability of depressive symptoms in the elderly. *Psychol. Med.* **34**, 471-479
382. Jick H, Kaye JA, Jick SS. (2004): Antidepressants and the risk of suicidal behaviors. *JAMA* **292**, 338-343
383. Joffe P, Larsen FS, Pedersen V, Ring-Larsen H, aes-Jorgensen T, Sidhu J. (1998): Single-dose pharmacokinetics of citalopram in patients with moderate renal insufficiency or hepatic cirrhosis compared with healthy subjects. *Eur. J. Clin. Pharmacol.* **54**, 237-242
384. Joffe RT, Singer W, Levitt AJ, MacDonald C. (1993): A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch. Gen. Psychiatry.* **50**, 387-393
385. John A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. (1999): Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin. Pharmacol. Ther.* **66**, 338-345
386. Jonsson A, Holmgren P, Ahlner J. (2004): Fatal intoxications in a Swedish forensic autopsy material during 1992-2002. *Forensic Sci. Int.* **143**, 53-59
387. Jönsson B and Bebbington PE. (1994): What price depression? The cost of depression and the cost-effectiveness of pharmacological treatment. *Br. J. Psychiatry.* **164**, 665-673
388. Jorm AF, Christensen H, Griffiths KM, Rodgers B. (2002): Effectiveness of complementary and self-help treatments for depression. *Med. J. Aust.* **176 Suppl**, S84-S96
389. Joyce PR, Mulder RT, Luty SE, McKenzie JM, Miller AL, Rogers GR, Kennedy MA. (2003): Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. *Int. J. Neuropsychopharmacol.* **6**, 339-346
390. Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, Rice JA, Keller MB. (1998): A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch. Gen. Psychiatry* **55**, 694-700
391. Kahn, L.S. & Halbreich, U. (2005): Estrogen effects in psychiatric disorders. Bergemann, N. & Riecher-Rössler, A. (eds.), pp. 145-173 (Springer Verlag, Wien, New York,
392. Kalb R, Trautmann-Sponsel RD, Kieser M. (2001): Efficacy and tolerability of hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients. A randomized double-blind multicenter clinical trial. *Pharmacopsychiatry* **34**, 96-103
393. Kamlet MS, Paul N, Greenhouse J, Kupfer D, Frank E, Wade M. (1995): Cost utility analysis of maintenance treatment for recurrent depression. *Control Clin. Trials.* **16**, 17-40

- 394. Kanner AM. (2003): When did neurologists and psychiatrists stop talking to each other? *Epilepsy Behav.* **4**, 597-601
- 395. Kanner AM. (2005a): Depression in epilepsy: a neurobiologic perspective. *Epilepsy Curr.* **5**, 21-27
- 396. Kanner AM. (2005b): Should neurologists be trained to recognize and treat comorbid depression of neurologic disorders? Yes. *Epilepsy Behav.* **6**, 303-311
- 397. Karasu TB, Docherty JP, Gelenberg A, Kupfer DJ, Merriam AE, Shadoan R. (1993): Practice guideline for major depressive disorder in adults. American Psychiatric Association. *American Journal of Psychiatry* **150**, 1-26
- 398. Kasper S. (2001): Hypericum perforatum--a review of clinical studies. *Pharmacopsychiatry* **34 Suppl 1**, S51-S55
- 399. Kasper S and Dienel A. (2002): Cluster analysis of symptoms during antidepressant treatment with Hypericum extract in mildly to moderately depressed out-patients. A meta-analysis of data from three randomized, placebo-controlled trials. *Psychopharmacology (Berl)* **164**, 301-308
- 400. Kasper S, Rogers SL, Madden PA, Joseph-Vanderpool JR, Rosenthal NE. (1990): The effects of phototherapy in the general population. *J. Affect. Disord.* **18**, 211-219
- 401. Kasper S and Schulz V. (1999): [High dose St. John's wort extract as a phytogenic antidepressant]. *Wien. Med. Wochenschr.* **149**, 191-196
- 402. Kato T. (2001): Molecular genetics of bipolar disorder. *Neurosci Res.* **40**, 105-113
- 403. Katona CL, Abou-Saleh MT, Harrison DA, Nairac BA, Edwards DR, Lock T, Burns RA, Robertson MM. (1995): Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *Br. J. Psychiatry.* **166**, 80-86
- 404. Kauffmann CD, Cheema MA, Miller BE. (2004): Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depress. Anxiety.* **19**, 59-62
- 405. Kavoussi RJ, Segraves RT, Hughes AR, Ascher JA, Johnston JA. (1997): Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J. Clin. Psychiatry* **58**, 532-537
- 406. Keller MB, Kocsis JH, Thase ME, Gelenberg AJ, Rush AJ, Koran L, Schatzberg A, Russell J, Hirschfeld R, Klein D, McCullough JP, Fawcett JA, Kornstein S, LaVange L, Harrison W. (1998): Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA.* **280**, 1665-1672
- 407. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. (2000): A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N. Engl. J. Med.* **342**, 1462-1470

408. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP. (2001): Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J. Am. Acad. Child Adolesc. Psychiatry* **40**, 762-772
409. Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, Mueller M, Bernstein H, Rasmussen K, O'Connor K, Smith G, Rush AJ, Biggs M, McClintock S, Bailine S, Malur C. (2005): Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. *Am. J. Psychiatry* **162**, 977-982
410. Kendler KS. (1998): Gender differences in the genetic epidemiology of major depression. *J Gend. Specif. Med.* **1**, 28-31
411. Kennedy SH, Andersen HF, Lam RW. (2006a): Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *J. Psychiatry Neurosci.* **31**, 122-131
412. Kennedy SH and Emsley R. (2006b): Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur. Neuropsychopharmacol.* **16**, 93-100
413. Kennedy SH, Lam RW, Cohen NL, Ravindran AV. (2001): Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. *Can. J. Psychiatry* **46 Suppl 1**, 38S-58S
414. Kent JM. (2000): SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* **355**, 911-918
415. Kessler RC. (2003): Epidemiology of women and depression. *J. Affect. Disord.* **74**, 5-13
416. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. (2003): The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* **289**, 3095-3105
417. Kessler RC, Soukup J, Davis RB, Foster DF, Wilkey SA, Van Rompay MI MI, Eisenberg DM. (2001): The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am. J. Psychiatry* **158**, 289-294
418. Khan A, Brodhead AE, Schwartz KA, Kolts RL, Brown WA. (2005): Sex differences in antidepressant response in recent antidepressant clinical trials. *J Clin Psychopharmacol.* **25**, 318-324
419. Khisti RT, Chopde CT, Jain SP. (2000): Antidepressant-like effect of the neurosteroid 3 α -hydroxy-5 α -pregnan-20-one in mice forced swim test. *Pharmacol. Biochem. Behav.* **67**, 137-143
420. Kielholz P. (1967): [The action spectra of antidepressive agents]. *Med. Welt.* **10**, 537-538

421. Kielholz P. (1979): The classification of depressions and the activity profile of the antidepressants. *Prog. Neuropsychopharmacol.* **3**, 59-63
422. Kim DK, Lim SW, Lee S, Sohn SE, Kim S, Hahn CG, Carroll BJ. (2000): Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport* **11**, 215-219
423. Kim HL, Streltzer J, Goebert D. (1999): St. John's wort for depression: a meta-analysis of well-defined clinical trials. *J. Nerv. Ment. Dis.* **187**, 532-538
424. Kimmel PL and Peterson RA. (2005): Depression in end-stage renal disease patients treated with hemodialysis: tools, correlates, outcomes, and needs. *Semin. Dial.* **18**, 91-97
425. Kind P and Sorensen J. (1995): Modelling the cost-effectiveness of the prophylactic use of SSRIs in the treatment of depression. *Int. Clin. Psychopharmacol.* **10 Suppl 1:41-8.**, 41-48
426. Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, Brockmoller J. (2004): Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol. Psychiatry* **9**, 442-473
427. Kitada M. (2003): Genetic polymorphism of cytochrome P450 enzymes in Asian populations: focus on CYP2D6. *Int. J Clin. Pharmacol. Res.* **23**, 31-35
428. Klysner R, Bent-Hansen J, Hansen HL, Lunde M, Pleidrup E, Poulsen DL, Andersen M, Petersen HE. (2002): Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. *Br. J. Psychiatry.* **181:29-35.**, 29-35
429. Knuuttila JE, Toronen P, Castren E. (2004): Effects of antidepressant drug imipramine on gene expression in rat prefrontal cortex. *Neurochem. Res.* **29**, 1235-1244
430. Kole MH, Swan L, Fuchs E. (2002): The antidepressant tianeptine persistently modulates glutamate receptor currents of the hippocampal CA3 commissural associational synapse in chronically stressed rats. *Eur. J. Neurosci.* **16**, 807-816
431. Kopell BH, Greenberg B, Rezai AR. (2004): Deep brain stimulation for psychiatric disorders. *J. Clin. Neurophysiol.* **21**, 51-67
432. Kornstein SG, Sloan DM, Thase ME. (2002): Gender-specific differences in depression and treatment response. *Psychopharmacol Bull.* **36**, 99-112
433. Koski A, Vuori E, Ojanpera I. (2005): Newer antidepressants: evaluation of fatal toxicity index and interaction with alcohol based on Finnish postmortem data. *Int. J. Legal Med.* **119**, 344-348
434. Kramer MS. (2002): Clinical update: substance P antagonists in patients with major depression. *Eur. Psychiatry* **17**, 10
435. Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, Reines SA, Liu G, Snively D, Wyatt-Knowles E, Hale JJ, Mills SG, MacCoss M, Swain CJ, Harrison T, Hill RG, Hefti F, Scolnick EM, Cascieri MA, Chicchi GG, Sadowski S, Williams AR, Hewson L, Smith D, Carlson EJ, Hargreaves RJ, Rupniak NMJ. (1998):

- Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* **281**, 1640-1645
436. Kramer MS, Winokur A, Kelsey J, Preskorn SH, Rothschild AJ, Snavely D, Ghosh K, Ball WA, Reines SA, Munjack D, Apter JT, Cunningham L, Kling M, Bari M, Getson A, Lee Y. (2004): Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology* **29**, 385-392
437. Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. (1997): Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am. J. Physiol* **272**, R1178-R1188
438. Krause P, Genz A, Knorr W. (1988): [Prospective study of the late sequelae of electroconvulsive treatment]. *Psychiatr. Neurol. Med. Psychol. (Leipz.)* **40**, 532-536
439. Krishnan KR and McDonald WM. (1995): Arteriosclerotic depression. *Med. Hypotheses* **44**, 111-115
440. Kroessler D. (1985): Relative efficacy rates for therapies of delusional depression. *Convuls. Ther.* **1**, 173-182
441. Krupnick JL, Sotsky SM, Simmens S, Moyer J, Elkin I, Watkins J, Pilkonis PA. (1996): The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin. Psychol.* **64**, 532-539
442. Krystal AD and Coffey CE. (1997): Neuropsychiatric considerations in the use of electroconvulsive therapy. *J. Neuropsychiatry Clin. Neurosci.* **9**, 283-292
443. Kuehner C. (2003): Gender differences in unipolar depression: an update of epidemiological findings and possible explanations. *Acta Psychiatr. Scand.* **108**, 163-174
444. Kuhs H, Farber D, Borgstadt S, Mrosek S, Tolle R. (1996): Amitriptyline in combination with repeated late sleep deprivation versus amitriptyline alone in major depression. A randomised study. *J. Affect. Disord.* **37**, 31-41
445. Kuhs H, Kemper B, Lippe-Neubauer U, Meyer-Dunker J, Tolle R. (1998): Repeated sleep deprivation once versus twice a week in combination with amitriptyline. *J. Affect. Disord.* **47**, 97-103
446. Kupfer DJ. (1991): Long-term treatment of depression. *J. Clin. Psychiatry* **52 Suppl**, 28-34
447. Kupfer DJ and Charney DS. (2003): "Difficult-to-treat depression". *Biol. Psychiatry* **53**, 633-634
448. Kupfer DJ and Rush AJ. (1983): Recommendations for depression publications. *Arch. Gen. Psychiatry* **40**, 1031
449. Laakmann G, Faltermaier-Temizel M, Bossert-Zaudig S, Baghai T. (1996): Are benzodiazepines antidepressants? *Psychopharmacology (Berl)* **124**, 291-292

- 450. Laakmann G, Schule C, Baghai T, Kieser M. (1998): St. John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* **31 Suppl 1**, 54-59
- 451. Lader MH. (1996): Tolerability and safety: essentials in antidepressant pharmacotherapy. *J Clin. Psychiatry* **57 Suppl 2**, 39-44
- 452. Lam RW, Levitan RD, Tam EM, Yatham LN, Lamoureux S, Zis AP. (1997): L-tryptophan augmentation of light therapy in patients with seasonal affective disorder. *Can. J. Psychiatry*. **42**, 303-306
- 453. Lambert MT, Trutia C, Petty F. (1998): Extrapyramidal adverse effects associated with sertraline. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **22**, 741-748
- 454. Landen M, Bjorling G, Agren H, Fahlen T. (1998): A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J. Clin. Psychiatry*. **59**, 664-668
- 455. Lauritzen L, Odgaard K, Clemmesen L, Lunde M, Ohrstrom J, Black C, Bech P. (1996): Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatr. Scand.* **94**, 241-251
- 456. Lave JR, Frank RG, Schulberg HC, Kamlet MS. (1998): Cost-effectiveness of treatments for major depression in primary care practice. *Arch. Gen. Psychiatry*. **55**, 645-651
- 457. Lawlor DA and Hopker SW. (2001): The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ* **322**, 763-767
- 458. Le Pen C, Levy E, Ravily V, Beuzen JN, Meurgey F. (1994): The cost of treatment dropout in depression. A cost-benefit analysis of fluoxetine vs. tricyclics. *J. Affect. Disord.* **31**, 1-18
- 459. Lecrubier Y, Clerc G, Didi R, Kieser M. (2002): Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *Am. J. Psychiatry* **159**, 1361-1366
- 460. Lederbogen F, Deuschle M, Heuser I. (1999): [Depression--a cardiovascular risk factor]. *Internist (Berl)* **40**, 1119-1121
- 461. Lederbogen F, Gilles M, Maras A, Hamann B, Colla M, Heuser I, Deuschle M. (2001): Increased platelet aggregability in major depression? *Psychiatry Res.* **102**, 255-261
- 462. LeDoux JE. (2000): Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23**, 155-184
- 463. LeDrew K, Phillips L, Hogan M, MacCallum A. (2005): Lamotrigine-induced neutropenia. *Can. J. Psychiatry* **50**, 242
- 464. Lee TM and Chan CC. (1999): Dose-response relationship of phototherapy for seasonal affective disorder: a meta-analysis. *Acta Psychiatr. Scand.* **99**, 315-323

- 465. Leff J, Vearnals S, Brewin CR, Wolff G, Alexander B, Asen E, Dayson D, Jones E, Chisholm D, Everitt B. (2000): The London Depression Intervention Trial. Randomised controlled trial of antidepressants v. couple therapy in the treatment and maintenance of people with depression living with a partner: clinical outcome and costs. *Br. J. Psychiatry*. **177:95-100.**, 95-100
- 466. Leinonen E, Skarstein J, Behnke K, Agren H, Helsdingen JT. (1999): Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. Nordic Antidepressant Study Group. *Int. Clin. Psychopharmacol* **14**, 329-337
- 467. Lemke MR. (2002): Effect of reboxetine on depression in Parkinson's disease patients. *J. Clin. Psychiatry* **63**, 300-304
- 468. Lenox-Smith A, Conway P, Knight C. (2004): Cost effectiveness of representatives of three classes of antidepressants used in major depression in the UK. *Pharmacoeconomics*. **22**, 311-319
- 469. Leonard, B.E. (2001): Antidepressants. Leonard, B.E. (ed.), pp. 109-120 (Birkhauser Verlag, Basel,
- 470. Leproult R, Van OA, L'hermite-Baleriaux M, Van CE, Copinschi G. (2005): Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. *Clin. Endocrinol. (Oxf)* **63**, 298-304
- 471. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL. (1996): Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**, 1527-1531
- 472. Lesch KP and Gutknecht L. (2004): Focus on The 5-HT_{1A} receptor: emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. *Int. J. Neuropsychopharmacol.* **7**, 381-385
- 473. Lesieur D, Leclerc V, Chavatte P, Marcot C, Renard P, Guardiola-Lemaitre B. (1998): Melatonin: a pertinent prototype for therapeutic intervention. *Therapie* **53**, 429-437
- 474. Leslie LK, Newman TB, Chesney PJ, Perrin JM. (2005): The Food and Drug Administration's deliberations on antidepressant use in pediatric patients. *Pediatrics* **116**, 195-204
- 475. Lieberman A. (2006): Depression in Parkinson's disease - a review. *Acta Neurol. Scand.* **113**, 1-8
- 476. Linde K, Berner M, Egger M, Mulrow C. (2005): St John's wort for depression: meta-analysis of randomised controlled trials. *Br. J. Psychiatry* **186**, 99-107
- 477. Linkowski P, Mendlewicz J, Kerkhofs M, Leclercq R, Goldstein J, Brasseur M, Copinschi G, van Cauter E. (1987): 24-hour profiles of adrenocorticotropin, cortisol, and growth hormone in major depressive illness: effect of antidepressant treatment. *J. Clin. Endocrinol. Metab.* **65**, 141-152

478. Lisanby SH, Luber B, Finck AD, Schroeder C, Sackeim HA. (2001a): Deliberate seizure induction with repetitive transcranial magnetic stimulation in nonhuman primates. *Arch. Gen. Psychiatry*. **58**, 199-200
479. Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. (2003a): Safety and Feasibility of Magnetic Seizure Therapy (MST) in Major Depression: Randomized Within-Subject Comparison with Electroconvulsive Therapy. *Neuropsychopharmacology* **28**, 1852-1865
480. Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. (2000): The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch. Gen. Psychiatry* **57**, 581-590
481. Lisanby SH, Morales O, Payne N, Kwon E, Fitzsimons L, Luber B, Nobler MS, Sackeim HA. (2003b): New developments in electroconvulsive therapy and magnetic seizure therapy. *CNS. Spectr.* **8**, 529-536
482. Lisanby SH, Pascual-Leone A, Sampson SM, Boylan LS, Burt T, Sackeim HA. (2001b): Augmentation of sertraline antidepressant treatment with transcranial magnetic stimulation. *Biological Psychiatry* **49**, 81S
483. Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA. (2001c): Magnetic seizure therapy of major depression. *Arch. Gen. Psychiatry* **58**, 303-305
484. Liu JLY, Maniadakis N, Gray A, Rayner M. (2002): The economic burden of coronary heart disease in the UK. *Heart* **88**, 597-603
485. Livingston MG and Livingston HM. (1996): Monoamine oxidase inhibitors. An update on drug interactions. *Drug Saf* **14**, 219-227
486. Loo CK, Mitchell PB, Croker VM, Malhi GS, Wen W, Gandevia SC, Sachdev PS. (2003): Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychol. Med.* **33**, 33-40
487. Loo H, Hale A, D'haenen H. (2002): Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int. Clin. Psychopharmacol.* **17**, 239-247
488. Lothgren M, Hemels M, Francois C, Jonsson B. (2004): A cost- effectiveness analysis of escitalopram as first line treatment of depression in Sweden. *Primary Care Psychiatry* **9**, 161
489. Lotufo-Neto F, Trivedi M, Thase ME. (1999): Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology* **20**, 226-247
490. Loving RT, Kripke DF, Shuchter SR. (2002): Bright light augments antidepressant effects of medication and wake therapy. *Depress. Anxiety*. **16**, 1-3
491. Lucena MI, Carvajal A, Andrade RJ, Velasco A. (2003): Antidepressant-induced hepatotoxicity. *Expert. Opin. Drug Saf* **2**, 249-262

- 492. Lucht MJ, Kleinschmidt R, Maier W, Rietschel M. (2000): Agranulocytosis during treatment with mianserin and venlafaxine. *J. Clin. Psychopharmacol.* **20**, 490-491
- 493. Ludwig J and Marcotte DE. (2005): Anti-depressants, suicide, and drug regulation. *J. Policy Anal. Manage.* **24**, 249-272
- 494. Mace S and Taylor D. (2000): Selective serotonin reuptake inhibitors: a review of efficacy and tolerability in depression. *Expert. Opin. Pharmacother.* **1**, 917-933
- 495. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. (2000): Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* **20**, 9104-9110
- 496. Malhotra AK, Murphy GM, Jr., Kennedy JL. (2004): Pharmacogenetics of psychotropic drug response. *Am. J. Psychiatry* **161**, 780-796
- 497. Malison RT, Anand A, Pelton GH, Kirwin P, Carpenter L, McDougale CJ, Heninger GR, Price LH. (1999): Limited efficacy of ketoconazole in treatment-refractory major depression. *J. Clin. Psychopharmacol.* **19**, 466-470
- 498. Mamdani MM, Parikh SV, Austin PC, Upshur RE. (2000a): Use of antidepressants among elderly subjects: trends and contributing factors. *Am. J. Psychiatry* **157**, 360-367
- 499. Mamdani MM, Parikh SV, Austin PC, Upshur RE. (2000b): Use of antidepressants among elderly subjects: trends and contributing factors. *Am. J. Psychiatry* **157**, 360-367
- 500. Manber R, Allen JJ, Morris MM. (2002): Alternative treatments for depression: empirical support and relevance to women. *J Clin. Psychiatry* **63**, 628-640
- 501. Manber R, Schnyer RN, Allen JJ, Rush AJ, Blasey CM. (2004): Acupuncture: a promising treatment for depression during pregnancy. *J Affect. Disord.* **83**, 89-95
- 502. Mancama D and Kerwin RW. (2003): Role of pharmacogenomics in individualising treatment with SSRIs. *CNS. Drugs* **17**, 143-151
- 503. Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL. (1997): Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol. Bull.* **33**, 149-154
- 504. Manji HK, Drevets WC, Charney DS. (2001): The cellular neurobiology of depression. *Nat. Med.* **7**, 541-547
- 505. Manji HK and Lenox RH. (1999): Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol. Psychiatry* **46**, 1328-1351
- 506. Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, Gray A, Zarate CA, Jr., Charney DS. (2003): Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol. Psychiatry.* **53**, 707-742

507. Mann JJ, Emslie G, Baldessarini RJ, Beardslee W, Fawcett JA, Goodwin FK, Leon AC, Meltzer HY, Ryan ND, Shaffer D, Wagner KD. (2006a): ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology* **31**, 473-492
508. Mann K, Hiemke C, Schmidt LG, Bates DW. (2006b): Appropriateness of therapeutic drug monitoring for antidepressants in routine psychiatric inpatient care. *Ther. Drug Monit.* **28**, 83-88
509. Manning DW, Markowitz JC, Frances AJ. (1992): A Review of Combined Psychotherapy and Pharmacotherapy in the Treatment of Depression. *J Psychother Pract Res* **1**, 103-116
510. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. (2004): Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* **292**, 807-820
511. Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, Wisniewski SR, Balasubramani GK, Trivedi MH, Rush AJ. (2005): Gender differences in depression: findings from the STAR*D study. *J Affect. Disord.* **87**, 141-150
512. Markowitz JC. (1993): Psychotherapy of the Postdysthymic Patient. *J Psychother Pract Res* **2**, 157-163
513. Markowitz JC, Kocsis JH, Bleiberg KL, Christos PJ, Sacks M. (2005): A comparative trial of psychotherapy and pharmacotherapy for "pure" dysthymic patients. *J. Affect. Disord.* **89**, 167-175
514. Martell, C.R., Addis, M.E. & Jacobson, N.S. (2001): Depression in Context: Strategies for Guided Action. W.W. Norton, New York
515. Martenyi F, Brown EB, Zhang H, Koke SC, Prakash A. (2002): Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. *Br. J. Psychiatry* **181**, 315-320
516. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. (2003): Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br. J. Psychiatry.* **182:480-91.**, 480-491
517. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, Evans S, Gunnell D. (2005): Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* **330**, 389
518. Martiny K, Lunde M, Uden M, Dam H, Bech P. (2005a): Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr. Scand.* **112**, 117-125
519. Martiny K, Lunde M, Uden M, Dam H, Bech P. (2005b): Adjunctive bright light in non-seasonal major depression: results from patient-reported symptom and well-being scales. *Acta Psychiatr. Scand.* **111**, 453-459

520. Mason J, Freemantle N, Eccles M. (2000): Fatal toxicity associated with antidepressant use in primary care. *Br. J Gen. Pract.* **50**, 366-370
521. Massana J, Moller HJ, Burrows GD, Montenegro RM. (1999): Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *Int. Clin. Psychopharmacol.* **14**, 73-80
522. Mattia C, Paoletti F, Coluzzi F, Boanelli A. (2002): New antidepressants in the treatment of neuropathic pain. A review. *Minerva Anesthesiol.* **68**, 105-114
523. Maurer-Spurej E, Pittendreigh C, Solomons K. (2004): The influence of selective serotonin reuptake inhibitors on human platelet serotonin. *Thromb. Haemost.* **91**, 119-128
524. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. (1999): Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry.* **156**, 675-682
525. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwab JM, Kennedy SH. (2005): Deep brain stimulation for treatment-resistant depression. *Neuron.* **45**, 651-660
526. McCall WV. (2001): Electroconvulsive therapy in the era of modern psychopharmacology. *Int. J. Neuropsychopharmacol.* **4**, 315-324
527. McCall WV, Reboussin DM, Weiner RD, Sackeim HA. (2000): Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch. Gen. Psychiatry* **57**, 438-444
528. McCullough JP, Jr. (2003): Treatment for chronic depression using Cognitive Behavioral Analysis System of Psychotherapy (CBASP). *J. Clin. Psychol.* **59**, 833-846
529. McCusker J, Cole M, Keller E, Bellavance F, Berard A. (1998): Effectiveness of treatments of depression in older ambulatory patients. *Arch. Intern. Med.* **158**, 705-712
530. McDaid D, Curran C, Knapp M. (2005): Promoting mental well-being in the workplace: A European policy perspective. *International Review of Psychiatry* **17**, 365-373
531. McDonald WM, Richard IH, DeLong MR. (2003): Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol. Psychiatry* **54**, 363-375
532. McEwen BS and Olie JP. (2005): Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol. Psychiatry* **10**, 525-537
533. Menza M, Marin H, Kaufman K, Mark M, Lauritano M. (2004): Citalopram treatment of depression in Parkinson's disease: the impact on anxiety, disability, and cognition. *J. Neuropsychiatry Clin. Neurosci.* **16**, 315-319
534. Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. (2003): A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch. Gen. Psychiatry* **60**, 904-912

535. Millan MJ, Brocco M, Gobert A, Dekeyne A. (2005): Anxiolytic properties of agomelatine, an antidepressant with melatonergic and serotonergic properties: role of 5-HT_{2C} receptor blockade. *Psychopharmacology (Berl)* **177**, 448-458
536. Millan MJ, Gobert A, Lejeune F, Dekeyne A, Newman-Tancredi A, Pasteau V, Rivet JM, Cussac D. (2003): The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine_{2C} receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J. Pharmacol. Exp. Ther.* **306**, 954-964
537. Miller P, Chilvers C, Dewey M, Fielding K, Gretton V, Palmer B, Weller D, Churchill R, Williams I, Bedi N, Duggan C, Lee A, Harrison G. (2003): Counseling versus antidepressant therapy for the treatment of mild to moderate depression in primary care: economic analysis. *Int. J. Technol. Assess. Health Care.* **19**, 80-90
538. Miniussi C, Bonato C, Bignotti S, Gazzoli A, Gennarelli M, Pasqualetti P, Tura GB, Ventriglia M, Rossini PM. (2005): Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clin. Neurophysiol.* **116**, 1062-1071
539. Misri S and Kostaras X. (2002): Benefits and risks to mother and infant of drug treatment for postnatal depression. *Drug Saf* **25**, 903-911
540. Mitchell AJ and Subramaniam H. (2005): Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am. J. Psychiatry* **162**, 1588-1601
541. Mitte K, Noack P, Steil R, Hautzinger M. (2005): A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J. Clin. Psychopharmacol.* **25**, 141-150
542. Mittmann N, Herrmann N, Einarson TR, Busto UE, Lanctot KL, Liu BA, Shulman KI, Silver IL, Narango CA, Shear NH. (1997): The efficacy, safety and tolerability of antidepressants in late life depression: a meta-analysis. *J. Affect. Disord.* **46**, 191-217
543. Möller, H.J. (1997): Therapieresistente Depressionen. Bauer, M. & Berghöfer, A. (eds.), pp. 3-15 (Springer, Berlin, Heidelberg,
544. Möller HJ. (2000): Are all antidepressants the same? *J. Clin. Psychiatry* **61 Suppl 6**, 24-28
545. Möller HJ. (2002): Anxiety associated with comorbid depression. *J Clin. Psychiatry* **63 Suppl 14**, 22-26
546. Möller HJ. (2003): Suicide, suicidality and suicide prevention in affective disorders. *Acta Psychiatr. Scand. Suppl.* 73-80
547. Möller HJ, Gallinat J, Hegerl U, Arato M, Janka Z, Pflug B, Bauer H. (1998): Double-blind, multicenter comparative study of sertraline and amitriptyline in hospitalized patients with major depression. *Pharmacopsychiatry* **31**, 170-177
548. Möller HJ, Grunze H, Broich K. (2006): Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants

- are the treatment of choice? A conceptual review. *Eur. Arch. Psychiatry Clin. Neurosci.* **256**, 1-16
549. Möller HJ, Kasper S, Muller H, Kissling W, Fuger J, Ruhrmann S. (1995): A controlled study of the efficacy and safety of mianserin and amitriptyline in depressive inpatients. *Pharmacopsychiatry* **28**, 249-252
550. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, Ledesma A, Bousoño M, Calcedo A, Carrasco JL, Ciudad J, Daniel E, de la GJ, Derecho J, Franco M, Gomez MJ, Macias JA, Martin T, Perez V, Sanchez JM, Sanchez S, Vicens E. (1997): SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J. Sex Marital Ther.* **23**, 176-194
551. Montgomery DB, Roberts A, Green M, Bullock T, Baldwin D, Montgomery SA. (1994): Lack of efficacy of fluoxetine in recurrent brief depression and suicidal attempts. *Eur. Arch. Psychiatry Clin. Neurosci.* **244**, 211-215
552. Montgomery SA. (1995): Safety of mirtazapine: a review. *Int. Clin. Psychopharmacol.* **10 Suppl 4**, 37-45
553. Montgomery SA. (1998): Chairman's overview. The place of reboxetine in antidepressant therapy. *J. Clin. Psychiatry* **59 Suppl 14**, 26-29
554. Montgomery SA. (1999): New developments in the treatment of depression. *J Clin. Psychiatry* **60 Suppl 14**, 10-15
555. Montgomery SA. (2005): Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int. J. Clin. Pract.* **59**, 1435-1440
556. Montgomery SA and Asberg M. (1979): A new depression scale designed to be sensitive to change. *Br. J. Psychiatry* **134**, 382-389
557. Montgomery SA, Huusom AK, Bothmer J. (2004a): A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* **50**, 57-64
558. Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. (2004b): Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int. Clin. Psychopharmacol.* **19**, 271-280
559. Montgomery SA, Prost JF, Solles A, Briley M. (1996): Efficacy and tolerability of milnacipran: an overview. *Int. Clin. Psychopharmacol.* **11 Suppl 4**, 47-51
560. Moore N, Verdoux H, Fantino B. (2005): Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int. Clin. Psychopharmacol.* **20**, 131-137
561. Moreno FA, Gelenberg AJ, Bachar K, Delgado PL. (1997): Pindolol augmentation of treatment-resistant depressed patients. *J. Clin. Psychiatry.* **58**, 437-439

562. Morgan ML, Cook IA, Rapkin AJ, Leuchter AF. (2005): Estrogen augmentation of antidepressants in perimenopausal depression: a pilot study. *J Clin. Psychiatry*. **66**, 774-780
563. Morgan O, Griffiths C, Baker A, Majeed A. (2004): Fatal toxicity of antidepressants in England and Wales, 1993-2002. *Health Stat. Q.* 18-24
564. Morrison A and Levy R. (2004): Toward individualized pharmaceutical care of East Asians: the value of genetic testing for polymorphisms in drug-metabolizing genes. *Pharmacogenomics*. **5**, 673-689
565. Moscrip TD, Terrace HS, Sackeim HA, Lisanby SH. (2005): Randomized controlled trial of the cognitive side-effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS). *Int. J. Neuropsychopharmacol.* **11**, 1-11
566. Mosimann UP, Schmitt W, Greenberg BD, Kosel M, Muri RM, Berkhoff M, Hess CW, Fisch HU, Schlaepfer TE. (2004): Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Res.* **126**, 123-133
567. Moskos M, Olson L, Halbern S, Keller T, Gray D. (2005): Utah youth suicide study: psychological autopsy. *Suicide Life Threat. Behav.* **35**, 536-546
568. Moskowitz H and Burns M. (1986): Cognitive performance in geriatric subjects after acute treatment with antidepressants. *Neuropsychobiology* **15 Suppl 1**, 38-43
569. Mottram P, Wilson K, Strobl J. (2006): Antidepressants for depressed elderly. *Cochrane. Database. Syst. Rev.* CD003491
570. Müller-Oerlinghausen, B., Ahrens, B. & Felber, W. (2006): Lithium in Neuropsychiatry - The Comprehensive Guide. Bauer, M., Grof, P. & Müller-Oerlinghausen, B. (eds.) (Informa Healthcare, Oxfordshire, OX14 4RN, U.K.,
571. Mulsant BH, Pollock BG, Nebes R, Miller MD, Sweet RA, Stack J, Houck PR, Bensasi S, Mazumdar S, Reynolds CF, III. (2001): A twelve-week, double-blind, randomized comparison of nortriptyline and paroxetine in older depressed inpatients and outpatients. *Am. J. Geriatr. Psychiatry* **9**, 406-414
572. Murphy BEP. (1991): Treatment of major depression with steroid suppressive drugs. *J. Steroid Biochem. Molec. Biol.* **39**, 239-244
573. Murphy BEP, Dhar V, Ghadirian AM, Chouinard G, Keller R. (1991): Response to steroid suppression in major depression resistant to antidepressant therapy. *J. Clin. Psychopharmacol.* **11**, 121-126
574. Murphy BEP, Filipini D, Ghadirian AM. (1993): Possible use of glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU 486. *J. Psychiatry Neurosci* **18**, 209-213
575. Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. (2005): Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception* **71**, 402-408

576. Musselman DL, Evans DL, Nemeroff CB. (1998): The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch. Gen. Psychiatry* **55**, 580-592
577. Naguib M and Koorn R. (2002): Interactions between psychotropics, anaesthetics and electroconvulsive therapy: implications for drug choice and patient management. *CNS. Drugs* **16**, 229-247
578. Nahas Z, Kozel FA, Li X, Anderson B, George MS. (2003): Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar. Disord.* **5**, 40-47
579. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS. (2005): Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J. Clin. Psychiatry* **66**, 1097-1104
580. National Institute of Mental Health. (1976): 028 CGI. Clinical Global Impressions. In: Guy, W. , Bonato, R. R. (Ed.) *Manual for the EDCEU Assessment Battery*, 2. Rev. Chevy Chase, Maryland, pp. 12-1 - 12-6
581. Navarro V, Gasto C, Torres X, Marcos T, Pintor L. (2001): Citalopram versus nortriptyline in late-life depression: a 12-week randomized single-blind study. *Acta Psychiatr. Scand.* **103**, 435-440
582. Nelson JC. (2000): Augmentation strategies in depression 2000. *J. Clin. Psychiatry.* **61 Suppl 2**, 13-19
583. Nelson JP and Benjamin L. (1989): Efficacy and Safety of Combined ECT and Tricyclic Antidepressant Drugs in the Treatment of Depressed Geriatric Patients. *Convuls. Ther.* **5**, 321-329
584. Nemeroff CB. (1994): Evolutionary trends in the pharmacotherapeutic management of depression. *J. Clin. Psychiatry* **55 Suppl**, 3-15
585. Nemeroff CB. (1996): The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol. Psychiatry* **1**, 336-342
586. Nemeroff CB, Gharabawi GM, Canuso CM. (2004): Augmentation with risperidone in chronic resistant depression: a double-blind placebo-controlled maintenance trial. *Neuropsychopharmacology* **29**, 5159
587. Nemeroff CB, Widerlöv E, Bisette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W. (1984): Elevated concentrations of CSF corticotropin-releasingfactor- like immunoreactivity in depressed patients. *Science* **226**, 1342-1343
588. Nemets B, Stahl Z, Belmaker RH. (2002): Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* **159**, 477-479
589. Nestler EJ. (1998): Antidepressant treatments in the 21st century. *Biol. Psychiatry* **44**, 526-533

- 590. Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S. (1996): Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol. Psychiatry* **39**, 16-21
- 591. Newhouse PA, Krishnan KR, Doraiswamy PM, Richter EM, Batzar ED, Clary CM. (2000): A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. *J. Clin. Psychiatry* **61**, 559-568
- 592. Niedermaier N, Bohrer E, Schulte K, Schlattmann P, Heuser I. (2004): Prevention and treatment of poststroke depression with mirtazapine in patients with acute stroke. *J. Clin. Psychiatry* **65**, 1619-1623
- 593. Nierenberg AA, Farabaugh AH, Alpert JE, Gordon J, Worthington JJ, Rosenbaum JF, Fava M. (2000): Timing of onset of antidepressant response with fluoxetine treatment. *Am. J Psychiatry* **157**, 1423-1428
- 594. Nijhuis IJ, Kok-Van Rooij GW, Bosschaart AN. (2001): Withdrawal reactions of a premature neonate after maternal use of paroxetine. *Arch. Dis. Child Fetal Neonatal Ed* **84**, F77
- 595. Nilsson FM and Kessing LV. (2004): Increased risk of developing stroke for patients with major affective disorder--a registry study. *Eur Arch. Psychiatry Clin. Neurosci.* **254**, 387-391
- 596. Nishizawa S, Benkelfat C, Young SN, Leyton M, Mzengeza S, de Montigny C, Blier P, Diksic M. (1997): Differences between males and females in rates of serotonin synthesis in human brain. *Proc. Natl. Acad. Sci. U. S. A.* **94**, 5308-5313
- 597. NN. (2001): Extrapyramidal effects of SSRI antidepressants. *Prescrire. Int.* **10**, 118-119
- 598. NN. (2002): Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Mov Disord.* **17**, 60-67
- 599. NN. (2004): Mirtazapine: seizures and neutropenia. *Prescrire. Int.* **13**, 58
- 600. Nonacs R and Cohen LS. (2003): Assessment and treatment of depression during pregnancy: an update. *Psychiatr. Clin. North Am.* **26**, 547-562
- 601. Normann C, Hummel B, Scharer LO, Horn M, Grunze H, Walden J. (2002): Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. *J. Clin. Psychiatry.* **63**, 337-344
- 602. North TC, McCullagh P, Tran ZV. (1990): Effect of exercise on depression. *Exerc. Sport Sci. Rev.* **18**, 379-415
- 603. Nuijten M, Hadjadjeba L, Evans C, van den BJ. (1998): Cost effectiveness of fluvoxamine in the treatment of recurrent depression in France. *Pharmacoeconomics.* **14**, 433-445
- 604. Nuijten MJ, Hardens M, Souetre E. (1995): A Markov process analysis comparing the cost effectiveness of maintenance therapy with citalopram versus standard therapy in major depression. *Pharmacoeconomics.* **8**, 159-168

605. Nutt DJ. (2002): The neuropharmacology of serotonin and noradrenaline in depression. *Int. Clin. Psychopharmacol.* **17 Suppl 1**, S1-12
606. O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, Mueller M, Snyder K, Bernstein H, Rush AJ, Fink M, Kellner C. (2001): The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *Am. J. Geriatr. Psychiatry* **9**, 382-390
607. O'Dwyer A-M, Lightman SL, Marks MN, Checkley SA. (1995): Treatment of major depression with metyrapone and hydrocortisone. *J. Affect. Disord.* **33**, 123-128
608. Obuchowicz E, Kowalski J, Labuzek K, Krysiak R, Pendzich J, Herman ZS. (2006): Amitriptyline and nortriptyline inhibit interleukin-1 release by rat mixed glial and microglial cell cultures. *Int. J. Neuropsychopharmacol.* **9**, 27-35
609. Ohberg A, Vuori E, Klaukka T, Lonnqvist J. (1998): Antidepressants and suicide mortality. *J Affect. Disord.* **50**, 225-233
610. Olfson M, Shaffer D, Marcus SC, Greenberg T. (2003): Relationship between antidepressant medication treatment and suicide in adolescents. *Arch. Gen. Psychiatry* **60**, 978-982
611. Olie JP and Emsley R. (2005): Confirmed clinical efficacy of agomelatine (25-50 mg) in major depression: two randomized, double-blind, placebo-controlled studies. *Eur Neuropsychopharmacol* **15**, S416
612. Olver JS, Burrows GD, Norman TR. (2001): Third-generation antidepressants: do they offer advantages over the SSRIs? *CNS. Drugs* **15**, 941-954
613. Oren DA, Wisner KL, Spinelli M, Epperson CN, Peindl KS, Terman JS, Terman M. (2002): An open trial of morning light therapy for treatment of antepartum depression. *Am. J. Psychiatry* **159**, 666-669
614. Oshima A and Higuchi T. (1999): Treatment guidelines for geriatric mood disorders. *Psychiatry Clin. Neurosci.* **53 Suppl**, S55-S59
615. Ottoson, J.O. & Fink, M. (2004): The Ethics in Electroconvulsive Therapy. Brunner/Routledge, New York
616. Ozcanli T, Unsalver B, Ozdemir S, Ozmen M. (2005): Sertraline- and mirtazapine-induced severe neutropenia. *Am. J. Psychiatry* **162**, 1386
617. Pacher P, Kohegyi E, Kecskemeti V, Furst S. (2001): Current trends in the development of new antidepressants. *Curr. Med. Chem.* **8**, 89-100
618. Padberg F and Möller HJ. (2003): Repetitive transcranial magnetic stimulation : does it have potential in the treatment of depression? *CNS. Drugs* **17**, 383-403
619. Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhael P, Ella R, Rupprecht P, Thoma H, Hampel H, Toschi N, Möller HJ. (2002): Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* **27**, 638-645

620. Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, Hampel H, Möller HJ. (1999): Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res.* **88**, 163-171
621. Papakostas GI. (2005): Augmentation of standard antidepressants with atypical antipsychotic agents for treatment-resistant major depressive disorder. *Essent. Psychopharmacol.* **6**, 209-220
622. Papakostas GI, Petersen TJ, Kinrys G, Burns AM, Worthington JJ, Alpert JE, Fava M, Nierenberg AA. (2005): Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. *J. Clin. Psychiatry* **66**, 1326-1330
623. Papakostas GI, Petersen TJ, Nierenberg AA, Murakami JL, Alpert JE, Rosenbaum JF, Fava M. (2004): Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J. Clin. Psychiatry* **65**, 217-221
624. Park RJ and Goodyer IM. (2000): Clinical guidelines for depressive disorders in childhood and adolescence. *Eur. Child Adolesc. Psychiatry* **9**, 147-161
625. Parry BL, Curran ML, Stuenkel CA, Yokimozo M, Tam L, Powell KA, Gillin JC. (2000): Can critically timed sleep deprivation be useful in pregnancy and postpartum depressions? *J Affect. Disord.* **60**, 201-212
626. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. (1996): Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* **347**, 233-237
627. Patel V, Chisholm D, Rabe-Hesketh S, Dias-Saxena F, Andrew G, Mann A. (2003): Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: a randomised, controlled trial. *Lancet.* **361**, 33-39
628. Patten SB and Metz LM. (1997): Depression in multiple sclerosis. *Psychother. Psychosom.* **66**, 286-292
629. Paul IA, Nowak G, Layer RT, Popik P, Skolnick P. (1994): Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. *J. Pharmacol. Exp. Ther.* **269**, 95-102
630. Pauwels PJ. (2000): Diverse signalling by 5-hydroxytryptamine (5-HT) receptors. *Biochem. Pharmacol.* **60**, 1743-1750
631. Paykel ES. (2001): Continuation and maintenance therapy in depression. *Br. Med. Bull.* **57:145-59.**, 145-159
632. Paykel ES and Priest RG. (1992): Recognition and management of depression in general practice: consensus statement. *BMJ.* **305**, 1198-1202
633. Pearlman C and Obedian E. (1995): ECT-valproic acid interaction. *Gen. Hosp. Psychiatry* **17**, 456-457

- 634. Pedersen AG. (2005): Escitalopram and suicidality in adult depression and anxiety. *Int. Clin. Psychopharmacol.* **20**, 139-143
- 635. Peet M and Horrobin DF. (2002): A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch. Gen. Psychiatry* **59**, 913-919
- 636. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. (2001): Depression and cardiac mortality: results from a community-based longitudinal study. *Arch. Gen. Psychiatry* **58**, 221-227
- 637. Peretti S, Judge R, Hindmarch I. (2000): Safety and tolerability considerations: tricyclic antidepressants vs. selective serotonin reuptake inhibitors. *Acta Psychiatr. Scand. Suppl* **403**, 17-25
- 638. Perez V, Soler J, Puigdemont D, Alvarez E, Artigas F. (1999): A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Grup de Recerca en Trastorns Afectius. *Arch. Gen. Psychiatry.* **56**, 375-379
- 639. Pesola GR and Avasarala J. (2002): Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. *J. Emerg. Med.* **22**, 235-239
- 640. Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG, Jr., Bernstein HJ, Biggs M, Bailine SH, Kellner CH. (2001): ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J. ECT.* **17**, 244-253
- 641. Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, Chatwin J, Goddard J, Thornett A, Smith H, Campbell M, Thompson C. (2005): A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine. *Health Technol. Assess.* **9**, 1-134, iii
- 642. Pevet P. (2002): Melatonin. *Dialogues Clin Neurosci* **4**, 57-72
- 643. Pezawas L, Angst J, Kasper S. (2005): Recurrent brief depression revisited. *Int. Rev. Psychiatry* **17**, 63-70
- 644. Pezawas L, Stamenkovic M, Kasper S. (2001): [Recurrent brief depressive episodes. Epidemiology, clinical aspects, diagnosis and therapy]. *Nervenarzt* **72**, 169-180
- 645. Philibert RA, Richards L, Lynch CF, Winokur G. (1995): Effect of ECT on mortality and clinical outcome in geriatric unipolar depression. *J. Clin. Psychiatry* **56**, 390-394
- 646. Philipp M, Kohnen R, Hiller KO. (1999): Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *BMJ* **319**, 1534-1538
- 647. Phillips SD and Ringo P. (1995): Phenelzine and venlafaxine interaction. *Am. J. Psychiatry* **152**, 1400-1401

648. Pincus HA, Zarin DA, Tanielian TL, Johnson JL, West JC, Pettit AR, Marcus SC, Kessler RC, McIntyre JS. (1999): Psychiatric patients and treatments in 1997: findings from the American Psychiatric Practice Research Network. *Arch. Gen. Psychiatry* **56**, 441-449
649. Pisani F, Spina E, Oteri G. (1999): Antidepressant drugs and seizure susceptibility: from in vitro data to clinical practice. *Epilepsia* **40 Suppl 10**, S48-S56
650. Post RM, Uhde TW, Roy-Byrne PP, Joffe RT. (1986): Antidepressant effects of carbamazepine. *Am. J Psychiatry* **143**, 29-34
651. Praschak-Rieder N, Neumeister A, Hesselmann B, Willeit M, Barnas C, Kasper S. (1997): Suicidal tendencies as a complication of light therapy for seasonal affective disorder: a report of three cases. *J. Clin. Psychiatry* **58**, 389-392
652. Prasko J, Horacek J, Klaschka J, Kosova J, Ondrackova I, Sipek J. (2002): Bright light therapy and/or imipramine for inpatients with recurrent non-seasonal depression. *Neuroendocrinol. Lett.* **23**, 109-113
653. Preskorn SH. (1995): Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J. Clin. Psychiatry* **56 Suppl 6**, 12-21
654. Price LH, Conwell Y, Nelson JC. (1983): Lithium augmentation of combined neuroleptic-tricyclic treatment in delusional depression. *Am. J. Psychiatry* **140**, 318-322
655. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. (2000): Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol* **3**,
656. Prien RF. (1990): Efficacy of continuation drug therapy of depression and anxiety: issues and methodologies. *J. Clin. Psychopharmacol.* **10**, 86S-90S
657. Prien RF and Kupfer DJ. (1986): Continuation drug therapy for major depressive episodes: how long should it be maintained? *Am. J. Psychiatry.* **143**, 18-23
658. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE. (1984): Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. *Arch. Gen. Psychiatry.* **41**, 1096-1104
659. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA. (1996): Resistance to antidepressant medications and short-term clinical response to ECT. *Am. J. Psychiatry* **153**, 985-992
660. Prudic J, Sackeim HA, Devanand DP. (1990): Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Res.* **31**, 287-296
661. Puozzo C, Albin H, Vincon G, Deprez D, Raymond JM, Amouretti M. (1998): Pharmacokinetics of milnacipran in liver impairment. *Eur. J. Drug Metab Pharmacokinet.* **23**, 273-279

- 662. Quitkin FM, Taylor BP, Kremer C. (2001): Does mirtazapine have a more rapid onset than SSRIs? *J. Clin. Psychiatry* **62**, 358-361
- 663. Rabheru K. (2001): The use of electroconvulsive therapy in special patient populations. *Can. J. Psychiatry* **46**, 710-719
- 664. Rabheru K and Persad E. (1997): A review of continuation and maintenance electroconvulsive therapy. *Can. J. Psychiatry* **42**, 476-484
- 665. Rabiner EA, Bhagwagar Z, Gunn RN, Sargent PA, Bench CJ, Cowen PJ, Grasby PM. (2001): Pindolol augmentation of selective serotonin reuptake inhibitors: PET evidence that the dose used in clinical trials is too low. *Am. J. Psychiatry*. **158**, 2080-2082
- 666. Ramaekers JG. (2003): Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J. Clin. Psychiatry* **64**, 20-29
- 667. Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG. (1995): Remission and relapse in major depression: a two-year prospective follow-up study. *Psychol. Med.* **25**, 1161-1170
- 668. Rampello L, Chiechio S, Nicoletti G, Alvano A, Vecchio I, Raffaele R, Malaguarnera M. (2004): Prediction of the response to citalopram and reboxetine in post-stroke depressed patients. *Psychopharmacology (Berl)* **173**, 73-78
- 669. Rampono J, Kristensen JH, Hackett LP, Paech M, Kohan R, Ilett KF. (2000): Citalopram and demethylcitalopram in human milk; distribution, excretion and effects in breast fed infants. *Br. J. Clin. Pharmacol.* **50**, 263-268
- 670. Rao KM, Gangadhar BN, Janakiramaiah N. (1993): Nonconvulsive Status Epilepticus after the Ninth Electroconvulsive Therapy. *Convuls. Ther.* **9**, 128-129
- 671. Rapaport MH, Schneider LS, Dunner DL, Davies JT, Pitts CD. (2003): Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J. Clin. Psychiatry* **64**, 1065-1074
- 672. Rasgon NL, Altshuler LL, Fairbanks LA, Dunkin JJ, Davtyan C, Elman S, Rapkin AJ. (2002): Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin. Psychiatry*. **63 Suppl 7:45-8.**, 45-48
- 673. Rasmussen KG, Sampson SM, Rummans TA. (2002): Electroconvulsive therapy and newer modalities for the treatment of medication-refractory mental illness. *Mayo Clin. Proc.* **77**, 552-556
- 674. Rasmussen NA, Schroder P, Olsen LR, Brodsgaard M, Unden M, Bech P. (2005): Modafinil augmentation in depressed patients with partial response to antidepressants: a pilot study on self-reported symptoms covered by the Major Depression Inventory (MDI) and the Symptom Checklist (SCL-92). *Nord. J Psychiatry*. **59**, 173-178
- 675. Raven PW, O'Dwyer A-M, Taylor NF, Checkley SA. (1996): The relationship between the effects of metyrapone treatment on depressed mood and urinary steroid profiles. *Psychoneuroendocrinol.* **21**, 277-286

676. Ravindran AV, Anisman H, Merali Z, Charbonneau Y, Telner J, Bialik RJ, Wiens A, Ellis J, Griffiths J. (1999): Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments. *Am. J. Psychiatry* **156**, 1608-1617
677. Rees AM, Austin MP, Parker G. (2005): Role of omega-3 fatty acids as a treatment for depression in the perinatal period. *Aust. N. Z. J. Psychiatry* **39**, 274-280
678. Reimherr FW, Hodges MR, Hill GE, Wong KC. (1977): Prolongation of muscle relaxant effects by lithium carbonate. *Am. J. Psychiatry* **134**, 205-206
679. Remick RA, Campos PE, Misri S, Miles JE, Van Wyck FJ. (1982): A comparison of the safety and efficacy of bupropion HCL and amitriptyline hcl in depressed outpatients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **6**, 523-527
680. Revicki DA, Brown RE, Keller MB, Gonzales J, Culpepper L, Hales RE. (1997): Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings. *J. Clin. Psychiatry*. **58**, 47-58
681. Reynolds CF, III, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, Mazumdar S, Houck PR, Dew MA, Stack JA, Pollock BG, Kupfer DJ. (1999): Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA*. **281**, 39-45
682. Richelson E. (2001): Pharmacology of antidepressants. *Mayo Clin. Proc.* **76**, 511-527
683. Ridout F, Meadows R, Johnsen S, Hindmarch I. (2003): A placebo controlled investigation into the effects of paroxetine and mirtazapine on measures related to car driving performance. *Hum. Psychopharmacol.* **18**, 261-269
684. Riecher-Rössler A. (2000): Psychische Erkrankungen bei Frauen - Einige Argumente für eine geschlechtersensible Psychiatrie und Psychotherapie. [Mental diseases in women - some arguments for a gender-sensitive psychiatry and psychotherapy]. *Z. Psychosom. Med Psychother.* **46**, 129-139
685. Riecher-Rössler, A, Kuhl, H & Bitzer, J. Psychische Störungen in Zeiten hormoneller Umstellung - eine selektive Übersichtsarbeit. (2006) *Neuropsychiatrie*. Ref Type: In Press
686. Rihmer Z, Appleby L, Rihmer A, Belso N. (2000): Decreasing suicide in Hungary. *Br. J Psychiatry*. **177**:84., 84
687. Risch NJ. (2000): Searching for genetic determinants in the new millennium. *Nature* **405**, 847-856
688. Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, . (1988): The Composite International Diagnostic Interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch. Gen. Psychiatry*. **45**, 1069-1077
689. Robinson DS, Lerfald SC, Bennett B, Laux D, Devereaux E, Kayser A, Corcella J, Albright D. (1991): Continuation and maintenance treatment of major depression with

- the monoamine oxidase inhibitor phenelzine: a double-blind placebo-controlled discontinuation study. *Psychopharmacol. Bull.* **27**, 31-39
690. Robinson WS. (1950): Ecological correlations and the behavior of individuals. *American Sociological Review* **15**, 351-357
691. Rocca P, Fonzo V, Ravizza L, Rocca G, Scotta M, Zanaldi E, Bogetto F. (2002): A comparison of paroxetine and amisulpride in the treatment of dysthymic disorder. *J. Affect. Disord.* **70**, 313-317
692. Rohland BM, Carroll BT, Jacoby RG. (1993): ECT in the treatment of the catatonic syndrome. *J. Affect. Disord.* **29**, 255-261
693. Rojo JE, Ros S, Aguera L, de la GJ, de Pedro JM. (2005): Combined antidepressants: clinical experience. *Acta Psychiatr. Scand. Suppl* 25-31, 36
694. Roman FJ, Pascaud X, Martin B, Vauche D, Junien JL. (1990): JO 1784, a potent and selective ligand for rat and mouse brain sigma-sites. *J. Pharm. Pharmacol.* **42**, 439-440
695. Romeo R, Patel A, Knapp M, Thomas C. (2004): The cost-effectiveness of mirtazapine versus paroxetine in treating people with depression in primary care. *Int. Clin. Psychopharmacol.* **19**, 125-134
696. Roose SP, Sackeim HA, Krishnan KR, Pollock BG, Alexopoulos G, Lavretsky H, Katz IR, Hakkarainen H. (2004): Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am. J. Psychiatry* **161**, 2050-2059
697. Roose SP and Schatzberg AF. (2005): The efficacy of antidepressants in the treatment of late-life depression. *J. Clin. Psychopharmacol.* **25**, S1-S7
698. Roschke J, Wolf C, Muller MJ, Wagner P, Mann K, Grozinger M, Bech S. (2000): The benefit from whole body acupuncture in major depression. *J Affect. Disord.* **57**, 73-81
699. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. (1998): Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol. Psychiatry* **44**, 77-87
700. Rosenthal NE, Sack DA, Carpenter CJ, Parry BL, Mendelson WB, Wehr TA. (1985): Antidepressant effects of light in seasonal affective disorder. *Am. J. Psychiatry* **142**, 163-170
701. Ross S and Williams D. (2005): Bupropion: risks and benefits. *Expert. Opin. Drug Saf* **4**, 995-1003
702. Rossello J and Bernal G. (1999): The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *J Consult Clin. Psychol.* **67**, 734-745

703. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. (2005): Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res* **137**,
704. Roth,A. & Fonagy,P. (2004): What Works for Whom? Guilford Press, New York
705. Rothschild AJ. (1996): Management of psychotic, treatment-resistant depression. *Psychiatr. Clin. North Am.* **19**, 237-252
706. Roxanas MG and Machado JF. (1998): Serotonin syndrome in combined moclobemide and venlafaxine ingestion. *Med. J. Aust.* **168**, 523-524
707. Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, Mansur C, Myczkowski ML, Moreno RA, Marcolin MA. (2005): Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry* **57**,
708. Rupprecht R. (1997): The neuropsychopharmacological potential of neuroactive steroids. *J. Psychiatr. Res.* **31**, 297-314
709. Rupprecht R, Baghai TC, Möller HJ. (2004): [New developments in pharmacotherapy of depression]. *Nervenarzt* **75**, 273-280
710. Rupprecht R and Holsboer F. (1999): Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci.* **22**, 410-416
711. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. (2000): Acute heart transplant rejection due to Saint John's wort. *Lancet* **355**, 548-549
712. Rush AJ. (1999): Strategies and tactics in the management of maintenance treatment for depressed patients. *J Clin. Psychiatry.* **60 Suppl 14:21-6; discussion 31-5.**, 21-26
713. Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, Trivedi MH, Suppes T, Miller AL, Biggs MM, Shores-Wilson K, Witte BP, Shon SP, Rago WV, Altshuler KZ. (2003a): Texas Medication Algorithm Project, phase 3 (TMAP-3): rationale and study design. *J. Clin. Psychiatry.* **64**, 357-369
714. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G. (2004): Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin. Trials* **25**, 119-142
715. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, Nahas Z, Haines S, Simpson RK, Jr., Goodman R. (2000): Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry* **47**,
716. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG. (2005a): Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol. Psychiatry* **58**, 347-354

- 717. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P, Howland R, Kling MA, Rittberg B, Carpenter L, Ninan P, Moreno F, Schwartz T, Conway C, Burke M, Barry JJ. (2005b): Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol. Psychiatry* **58**, 355-363
- 718. Rush,A.J. & Thase,M.E. (1999): Maj,M. & Sartorius,N. (eds.), pp. 161-206 (John Wiley & Sons, Chichester,
- 719. Rush AJ, Thase ME, Dube S. (2003b): Research issues in the study of difficult-to-treat depression. *Biol. Psychiatry* **53**, 743-753
- 720. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M. (2006): Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N. Engl. J. Med.* **354**, 1231-1242
- 721. Rybakowski JK, Suwalska A, Chlopocka-Wozniak M. (1999): Potentiation of antidepressants with lithium or carbamazepine in treatment-resistant depression. *Neuropsychobiology* **40**, 134-139
- 722. Saarto T and Wiffen PJ. (2005): Antidepressants for neuropathic pain. *Cochrane. Database. Syst. Rev.* CD005454
- 723. Sachdev PS and Sachdev J. (2005): Long-term outcome of neurosurgery for the treatment of resistant depression. *J. Neuropsychiatry Clin. Neurosci.* **17**, 478-485
- 724. Sackeim HA. (2001): The definition and meaning of treatment-resistant depression. *J. Clin. Psychiatry* **62 Suppl 16**, 10-17
- 725. Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S. (1987): Effects of electrode placement on the efficacy of titrated, low-dose ECT. *Am. J. Psychiatry* **144**, 1449-1455
- 726. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM. (1993): Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N. Engl. J. Med.* **328**, 839-846
- 727. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J. (2000): A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch. Gen. Psychiatry* **57**, 425-434
- 728. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson RK, Jr., Goodman RR. (2001): Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* **25**, 713-728
- 729. Sairanen M, Lucas G, Ernfors P, Castren M, Castren E. (2005): Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. *J. Neurosci.* **25**, 1089-1094

730. Samuelian JC and Hackett D. (1998): A randomized, double-blind, parallel-group comparison of venlafaxine and clomipramine in outpatients with major depression. *J. Psychopharmacol.* **12**, 273-278
731. Sanacora G, Mason GF, Krystal JH. (2000): Impairment of GABAergic transmission in depression: new insights from neuroimaging studies. *Crit Rev. Neurobiol.* **14**, 23-45
732. Sanchez C, Bogeso KP, Ebert B, Reines EH, Braestrup C. (2004): Escitalopram versus citalopram: the surprising role of the R-enantiomer. *Psychopharmacology (Berl)* **174**, 163-176
733. Santarelli L, Gobbi G, Debs PC, Sibille ET, Blier P, Hen R, Heath MJ. (2001): Genetic and pharmacological disruption of neurokinin 1 receptor function decreases anxiety-related behaviors and increases serotonergic function. *Proc. Natl. Acad. Sci. U. S. A* **98**, 1912-1917
734. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. (2003): Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301**, 805-809
735. Sartorius A and Henn FA. (2005a): [Continuation ECT]. *Psychiatr. Prax.* **32**, 408-411
736. Sartorius A and Henn FA. (2005b): [Treating depressive disorders with continuation electroconvulsive therapy.]. *Nervenarzt* **76**, 1363-1369
737. Sartorius A, Wolf J, Henn FA. (2005c): Lithium and ECT--concurrent use still demands attention: three case reports. *World J. Biol. Psychiatry* **6**, 121-124
738. Sartorius N. (1974): Description and classification of depressive disorders. Contributions for the definition of the therapy-resistance and of therapy resistant depressions. *Pharmakopsychiatr. Neuropsychopharmakol.* **7**, 76-79
739. Saxena S, Paraje G, Sharan P, Karam G, Sadana R. (2006): The 10/90 divide in mental health research: trends over a 10-year period. *Br. J. Psychiatry* **188**, 81-82
740. scamps-Francois C, Yous S, Chavatte P, Audinot V, Bonnaud A, Boutin JA, Delagrangé P, Bennejean C, Renard P, Lesieur D. (2003): Design and synthesis of naphthalenic dimers as selective MT1 melatonergic ligands. *J. Med. Chem.* **46**, 1127-1129
741. Schatzberg AF, Kremer C, Rodrigues HE, Murphy GM, Jr. (2002): Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am. J. Geriatr. Psychiatry* **10**, 541-550
742. Scheibe S, Preuschhof C, Cristi C, Bagby RM. (2003): Are there gender differences in major depression and its response to antidepressants? *J Affect. Disord.* **75**, 223-235
743. Schilgen B and Tolle R. (1980): Partial sleep deprivation as therapy for depression. *Arch. Gen. Psychiatry* **37**, 267-271
744. Schillevoort I, van Puijenbroek EP, de BA, Roos RA, Jansen PA, Leufkens HG. (2002): Extrapyramidal syndromes associated with selective serotonin reuptake

- inhibitors: a case-control study using spontaneous reports. *Int. Clin. Psychopharmacol.* **17**, 75-79
745. Schirren CA and Baretton G. (2000): Nefazodone-induced acute liver failure. *Am. J. Gastroenterol.* **95**, 1596-1597
746. Schmauss M, Kapfhammer HP, Meyr P, Hoff P. (1988): Combined MAO-inhibitor and tri- (tetra) cyclic antidepressant treatment in therapy resistant depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **12**, 523-532
747. Schneider LS, Nelson JC, Clary CM, Newhouse P, Krishnan KR, Shiovitz T, Weihs K. (2003): An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. *Am. J. Psychiatry* **160**, 1277-1285
748. Schneider LS, Small GW, Clary CM. (2001): Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am. J. Geriatr. Psychiatry.* **9**, 393-399
749. Schneider LS, Small GW, Hamilton SH, Bystritsky A, Nemeroff CB, Meyers BS. (1997): Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *Am. J. Geriatr. Psychiatry.* **5**, 97-106
750. Schou M. (1995): Prophylactic lithium treatment of unipolar and bipolar manic-depressive illness. *Psychopathology.* **28 Suppl 1:81-5.**, 81-85
751. Schrader E. (2000): Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int. Clin. Psychopharmacol.* **15**, 61-68
752. Schüle C, Zwanzger P, Baghai T, Mikhael P, Thoma H, Möller HJ, Rupprecht R, Padberg F. (2003): Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: an open follow-up study. *J. Psychiatr. Res.* **37**, 145-153
753. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. (2000): Association between depression and mortality in older adults: the Cardiovascular Health Study. *Arch. Intern. Med.* **160**, 1761-1768
754. Schulze TG, Muller DJ, Krauss H, Scherk H, Ohlraun S, Syagailo YV, Windemuth C, Neidt H, Grassle M, Papassotiropoulos A, Heun R, Nothen MM, Maier W, Lesch KP, Rietschel M. (2000): Association between a functional polymorphism in the monoamine oxidase A gene promoter and major depressive disorder. *Am. J. Med. Genet.* **96**, 801-803
755. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M. (2005): Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *Br J Psychiatry* **186**,
756. Schuurman AG, Van den AM, Ensink KT, Metsemakers JF, Knottnerus JA, Leentjens AF, Buntinx F. (2002): Increased risk of Parkinson's disease after depression: a retrospective cohort study. *Neurology* **58**, 1501-1504

757. Schwarz MJ and Ackenheil M. (2002): The role of substance P in depression: therapeutic indications. *Dialogues. Clin. Neurosci.* **4**, 21-29
758. Scott AI and Freeman CP. (1992): Edinburgh primary care depression study: treatment outcome, patient satisfaction, and cost after 16 weeks. *BMJ.* **304**, 883-887
759. Segrave R and Nathan PJ. (2005): Pindolol augmentation of selective serotonin reuptake inhibitors: accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. *Hum. Psychopharmacol.* **20**, 163-174
760. Serebruany VL. (2006): Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? *Am. J. Med.* **119**, 113-116
761. Serretti A, Artioli P, Quartesan R. (2005): Pharmacogenetics in the treatment of depression: pharmacodynamic studies. *Pharmacogenet. Genomics* **15**, 61-67
762. Serretti A, Cusin C, Lattuada E, di Bella D, Catalano M, Smeraldi E. (1999): Serotonin transporter gene (5-HTTLPR) is not associated with depressive symptomatology in mood disorders A Serretia, C Cusin, E Lattuada, D Di Bella, M Catalano and E Smeraldi . *Mol. Psychiatry* **4**, 280-283
763. Shea MT, Widiger TA, Klein MH. (1992): Comorbidity of personality disorders and depression: implications for treatment. *J. Consult Clin. Psychol.* **60**, 857-868
764. Sheehan JD and Shelley RK. (1990): Leucopenia secondary to carbamazepine despite concurrent lithium treatment. *Br. J. Psychiatry* **157**, 911-912
765. Sheline YI, Gado MH, Kraemer HC. (2003): Untreated depression and hippocampal volume loss. *Am. J. Psychiatry* **160**, 1516-1518
766. Shelton RC, Keller MB, Gelenberg A, Dunner DL, Hirschfeld R, Thase ME, Russell J, Lydiard RB, Crits-Cristoph P, Gallop R, Todd L, Hellerstein D, Goodnick P, Keitner G, Stahl SM, Halbreich U. (2001a): Effectiveness of St John's wort in major depression: a randomized controlled trial. *JAMA* **285**, 1978-1986
767. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, Buras WR, Bymaster FP, Zhang W, Spencer KA, Feldman PD, Meltzer HY. (2001b): A novel augmentation strategy for treating resistant major depression. *Am. J. Psychiatry.* **158**, 131-134
768. Shelton RC, Williamson DJ, Corya SA, Sanger TM, Van Campen LE, Case M, Briggs SD, Tollefson GD. (2005): Olanzapine/Fluoxetine Combination for Treatment-Resistant Depression: A Controlled Study of SSRI and Nortriptyline Resistance. *J. Clin. Psychiatry.* **66**, 1289-1297
769. Shepherd G, Velez LI, Keyes DC. (2004): Intentional bupropion overdoses. *J. Emerg. Med.* **27**, 147-151
770. Shim YS and Yang DW. (2006): Depression as prognostic factor: 6 months follow-up in a geriatric institution. *Arch. Gerontol. Geriatr.* .,

- 771. Silva RC and Brandao ML. (2000): Acute and chronic effects of gepirone and fluoxetine in rats tested in the elevated plus-maze: an ethological analysis. *Pharmacol. Biochem. Behav.* **65**, 209-216
- 772. Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. (2005): Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot. Essent. Fatty Acids* **72**, 211-218
- 773. Simeon JG, Dinicola VF, Ferguson HB, Copping W. (1990): Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **14**, 791-795
- 774. Simon GE, Heiligenstein J, Revicki D, VonKorff M, Katon WJ, Ludman E, Grothaus L, Wagner E. (1999a): Long-term outcomes of initial antidepressant drug choice in a "real world" randomized trial. *Arch. Fam. Med.* **8**, 319-325
- 775. Simon GE, Revicki D, Heiligenstein J, Grothaus L, VonKorff M, Katon WJ, Hylan TR. (2000a): Recovery from depression, work productivity, and health care costs among primary care patients. *Gen. Hosp. Psychiatry.* **22**, 153-162
- 776. Simon GE, Savarino J, Operskalski B, Wang PS. (2006): Suicide risk during antidepressant treatment. *Am. J. Psychiatry* **163**, 41-47
- 777. Simon GE, Von Korff M, Ludman EJ, Katon WJ, Rutter C, Unutzer J, Lin EH, Bush T, Walker E. (2002): Cost-effectiveness of a program to prevent depression relapse in primary care. *Med. Care.* **40**, 941-950
- 778. Simon GE, VonKorff M, Heiligenstein JH, Revicki DA, Grothaus L, Katon W, Wagner EH. (1996): Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine vs tricyclic antidepressants. *JAMA.* **275**, 1897-1902
- 779. Simon GE, VonKorff M, Piccinelli M, Fullerton C, Ormel J. (1999b): An international study of the relation between somatic symptoms and depression. *N. Engl. J. Med.* **341**, 1329-1335
- 780. Simon GE, VonKorff M, Rutter C, Wagner E. (2000b): Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. *BMJ.* **320**, 550-554
- 781. Simon JS and Nemeroff CB. (2005): Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. *J. Clin. Psychiatry.* **66**, 1216-1220
- 782. Simpson HB, Liebowitz MR, Foa EB, Kozak MJ, Schmidt AB, Rowan V, Petkova E, Kjernisted K, Huppert JD, Franklin ME, Davies SO, Campeas R. (2004): Post-treatment effects of exposure therapy and clomipramine in obsessive-compulsive disorder. *Depress. Anxiety.* **19**, 225-233
- 783. Singh NA, Clements KM, Singh MA. (2001): The efficacy of exercise as a long-term antidepressant in elderly subjects: a randomized, controlled trial. *J. Gerontol. A Biol. Sci. Med. Sci.* **56**, M497-M504

- 784. Sir A, D'Souza RF, Uguz S, George T, Vahip S, Hopwood M, Martin AJ, Lam W, Burt T. (2005): Randomized Trial of Sertraline Versus Venlafaxine XR in Major Depression: Efficacy and Discontinuation Symptoms. *J. Clin. Psychiatry* **66**, 1312-1320
- 785. Slattery DA, Hudson AL, Nutt DJ. (2004): Invited review: the evolution of antidepressant mechanisms. *Fundam. Clin. Pharmacol.* **18**, 1-21
- 786. Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C. (1999): Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. A placebo-controlled trial. *Neuropsychopharmacology* **20**, 380-385
- 787. Smith CA and Hay PP. (2005): Acupuncture for depression. *Cochrane. Database. Syst. Rev.* CD004046
- 788. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. (2002): Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br. J. Psychiatry* **180**, 396-404
- 789. Smith RS. (1991): The macrophage theory of depression. *Med. Hypotheses* **35**, 298-306
- 790. Sokolski KN, Conney JC, Brown BJ, DeMet EM. (2004): Once-daily high-dose pindolol for SSRI-refractory depression. *Psychiatry Res.* **125**, 81-86
- 791. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, Coryell W, Warshaw M, Turvey C, Maser JD, Endicott J. (2000): Multiple recurrences of major depressive disorder. *Am. J. Psychiatry.* **157**, 229-233
- 792. Sondergard L, Kvist K, Andersen PK, Kessing LV. (2006): Do antidepressants precipitate youth suicide? A nationwide pharmacoepidemiological study. *Eur. Child Adolesc. Psychiatry*
- 793. Sontrop J and Campbell MK. (2006): omega-3 polyunsaturated fatty acids and depression: A review of the evidence and a methodological critique. *Prev. Med.* **42**, 4-13
- 794. Sotsky SM, Glass DR, Shea MT, Pilkonis PA, Collins JF, Elkin I, Watkins JT, Imber SD, Leber WR, Moyer J, . (1991): Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. *Am. J Psychiatry* **148**, 997-1008
- 795. Souza FG and Goodwin GM. (1991): Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. *Br. J. Psychiatry.* **158:666-75.**, 666-675
- 796. Sovner R and Fogelman S. (2002): Ketoconazole therapy for atypical depression. *J. Clin. Psychiatry* **57**, 227-228
- 797. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, Langfitt JT, Walczak TS, Pacia SV, Ebrahimi N, Frobish D. (2003): Initial outcomes in the Multicenter Study of Epilepsy Surgery. *Neurology* **61**, 1680-1685

798. Stahl SM. (1998): Selecting an antidepressant by using mechanism of action to enhance efficacy and avoid side effects. *J. Clin. Psychiatry* **59**, 23-29
799. Stahl SM. (2001): Effects of estrogen on the central nervous system. *J. Clin. Psychiatry* **62**, 317-318
800. Stahl SM, Grady MM, Moret C, Briley M. (2005): SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS. Spectr.* **10**, 732-747
801. Starkstein SE, Petracca G, Teson A, Chemerinski E, Merello M, Migliorelli R, Leiguarda R. (1996): Catatonia in depression: prevalence, clinical correlates, and validation of a scale. *J. Neurol. Neurosurg. Psychiatry* **60**, 326-332
802. Stassen HH and Angst J. (1998): Delayed Onset of Action of Antidepressants- Fact or Fiction? *CNS. Drugs* **9**, 177-184
803. Stein DJ, Zungu-Dirwayi N, Der Linden GJ, Seedat S. (2000): Pharmacotherapy for posttraumatic stress disorder. *Cochrane. Database. Syst. Rev.* CD002795
804. Steinacher L, Vandel P, Zullino DF, Eap CB, Brawand-Amey M, Baumann P. (2002): Carbamazepine augmentation in depressive patients non-responding to citalopram: a pharmacokinetic and clinical pilot study. *Eur. Neuropsychopharmacol.* **12**, 255-260
805. Stotz G, Woggon B, Angst J. (1999): Psychostimulants in the therapy of treatment-resistant depression. Review of the literature and findings from a retrospective study in 65 depressed patients. *Dialogues. Clin. Neurosci.* **1**, 165-174
806. Stout SC, Owens MJ, Nemeroff CB. (2001): Neurokinin(1) receptor antagonists as potential antidepressants. *Annu. Rev. Pharmacol. Toxicol.* **41**, 877-906
807. Sturm R and Wells KB. (1995): How can care for depression become more cost-effective? *JAMA.* **273**, 51-58
808. Sugahara H, Tokunaga S, Kondo T, Akamine M, Yoshimasu K, Fujisawa K, Fukudome K, Kanemitsu Y, Kubo C. (2005): Comparative adherence to antidepressant drugs in a non-psychiatric outpatient clinic setting in Japan. *Primary Care & Community Psychiatry* **10**, 57-62
809. Sulser F, Vetulani J, Mobley PL. (1978): Mode of action of antidepressant drugs. *Biochem. Pharmacol.* **27**, 257-261
810. Suri A, Reddy S, Gonzales C, Knadler MP, Branch RA, Skinner MH. (2005): Duloxetine pharmacokinetics in cirrhotics compared with healthy subjects. *Int. J. Clin. Pharmacol. Ther.* **43**, 78-84
811. Suri RA, Altshuler LL, Burt VK, Hendrick VC. (1998): Managing psychiatric medications in the breast-feeding woman. *Medscape. Womens Health* **3**, 1
812. Sussman N, Ginsberg DL, Bikoff J. (2001): Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J. Clin. Psychiatry* **62**, 256-260

813. Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, El YM, Vaugeois JM, Nomikos GG, Greengard P. (2006): Alterations in 5-HT_{1B} receptor function by p11 in depression-like states. *Science* **311**, 77-80
814. Svestka J, Rysanek R, Ceskova E. (1990): Sodium valproate in the treatment of endogenous depression. *Activ Nerv Super* **32**, 231-232
815. Szanto K, Mulsant BH, Houck P, Dew MA, Reynolds CF, III. (2003): Occurrence and course of suicidality during short-term treatment of late-life depression. *Arch Gen Psychiatry*. **60**, 610-617
816. Szegedi A, Kohnen R, Dienel A, Kieser M. (2005a): Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. *BMJ* **330**, 503
817. Szegedi A and Schwertfeger N. (2005b): Mirtazapine: a review of its clinical efficacy and tolerability. *Expert. Opin. Pharmacother.* **6**, 631-641
818. Tamminga CA, Nemeroff CB, Blakely RD, Brady L, Carter CS, Davis KL, Dingledine R, Gorman JM, Grigoriadis DE, Henderson DC, RB BI, Killen J, Laughren TP, McDonald WM, GM Jr MM, Paul SM, Rudorfer MV, Sausville E, Schatzberg AF, Scolnick EM, Suppes T. (2002): Developing novel treatments for mood disorders: accelerating discovery. *Biol. Psychiatry* **52**, 589-609
819. Tardiff K, Marzuk PM, Leon AC. (2002): Role of antidepressants in murder and suicide. *Am. J. Psychiatry* **159**, 1248-1249
820. Taylor DP, Carter RB, Eison AS, Mullins UL, Smith HL, Torrente JR, Wright RN, Yocca FD. (1995): Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. *J. Clin. Psychiatry* **56 Suppl 6**, 3-11
821. Taylor MA and Fink M. (2003): Catatonia in psychiatric classification: a home of its own. *Am. J. Psychiatry* **160**, 1233-1241
822. Taylor, M.A. & Fink, M. (2006): *Melancholia: The Diagnosis, Pathophysiology and Treatment of Depressive Illness*. Cambridge University Press, Cambridge
823. Terman M and Terman JS. (2005): Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS. Spectr.* **10**, 647-663
824. Thakore JH and Dinan TG. (1995): Cortisol synthesis inhibition: A new treatment strategy for the clinical and endocrine manifestations of depression. *Biol. Psychiatry* **37**, 364-368
825. Thase ME. (1999a): Antidepressant treatment of the depressed patient with insomnia. *J. Clin. Psychiatry* **60 Suppl 17**, 28-31
826. Thase ME. (1999b): Redefining antidepressant efficacy toward long-term recovery. *J. Clin. Psychiatry*. **60 Suppl 6**, 15-19
827. Thase ME. (2006): Managing depressive and anxiety disorders with escitalopram. *Expert. Opin. Pharmacother.* **7**, 429-440

828. Thase ME, Greenhouse JB, Frank E, Reynolds CF, Grochocinski V, Kupfer DJ. (1997): Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch. Gen. Psychiatry* **54**, 1009-1015
829. Thase ME, Mallinger AG, McKnight D, Himmelhoch JM. (1992): Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *Am. J. Psychiatry* **149**, 195-198
830. Thase ME, Trivedi MH, Rush AJ. (1995): MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* **12**, 185-219
831. Thiels C, Linden M, Grieger F, Leonard J. (2005): Gender differences in routine treatment of depressed outpatients with the selective serotonin reuptake inhibitor sertraline. *Int Clin Psychopharmacol.* **20**, 1-7
832. Thomas CM and Morris S. (2003): Cost of depression among adults in England in 2000. *Br. J. Psychiatry.* **183:514-9.**, 514-519
833. Thomas CS and Read DA. (1990): Mianserin, agranulocytosis, and suicide. *Lancet* **336**, 1511
834. Tollefson GD, Bosomworth JC, Heiligenstein JH, Potvin JH, Holman S. (1995): A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. *Int. Psychogeriatr.* **7**, 89-104
835. Tossani E, Cassano P, Fava M. (2005): Depression and renal disease. *Semin. Dial.* **18**, 73-81
836. Tran PV, Bymaster FP, McNamara RK, Potter WZ. (2003): Dual monoamine modulation for improved treatment of major depressive disorder. *J. Clin. Psychopharmacol.* **23**, 78-86
837. Trautmann-Sponsel RD and Dienel A. (2004): Safety of Hypericum extract in mildly to moderately depressed outpatients: a review based on data from three randomized, placebo-controlled trials. *J. Affect. Disord.* **82**, 303-307
838. Trescoli-Serrano C and Smith NK. (1996): Sertraline-induced agranulocytosis. *Postgrad. Med. J.* **72**, 446
839. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF, Shores-Wilson K, Rush AJ. (2006): Medication augmentation after the failure of SSRIs for depression. *N. Engl. J. Med.* **354**, 1243-1252
840. Trivedi MH, Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, Key T, Biggs MM, Shores-Wilson K, Witte B, Suppes T, Miller AL, Altshuler KZ, Shon SP. (2004): Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. *Arch. Gen. Psychiatry.* **61**, 669-680

841. Tuma S, Strubbe JJ, Mocaer E, Koolhaas JM. (2002): S20098 affects the free-running rhythms of body temperature and activity and decreases light-induced phase delay of circadian rhythms of the rat. *Chronobiol. Int.* **18**, 781-799
842. Tzimas GN, Dion B, Deschenes M. (2003): Early onset, nefazodone-induced fulminant hepatic failure. *Am. J. Gastroenterol.* **98**, 1663-1664
843. Uebelhack R, Gruenwald J, Graubaum HJ, Busch R. (2004): Efficacy and tolerability of Hypericum extract STW 3-VI in patients with moderate depression: a double-blind, randomized, placebo-controlled clinical trial. *Adv. Ther.* **21**, 265-275
844. Ural AU, Avcu F, Gokcil Z, Nevruz O, Cetin T. (2005): Leucopenia and thrombocytopenia possibly associated with lamotrigine use in a patient. *Epileptic. Disord.* **7**, 33-35
845. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. (2004): Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS. Drugs* **18**, 1119-1132
846. Van Amerongen AP, Ferrey G, Tournoux A. (2002): A randomised, double-blind comparison of milnacipran and imipramine in the treatment of depression. *J. Affect. Disord.* **72**, 21-31
847. van Baardewijk M, Vis PM, Einarson TR. (2005): Cost effectiveness of duloxetine compared with venlafaxine-XR in the treatment of major depressive disorder. *Curr. Med. Res. Opin.* **21**, 1271-1279
848. van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. (1997): A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. *J. Nerv. Ment. Dis.* **185**, 510-516
849. van Calker D. & Berger, M. (2000): Affektive Erkrankungen. Richtlinienentwurf der DGPPN. Steinkopff, Darmstadt
850. van Moffaert M, de WJ, Vereecken A, Dierick M, Evrard JL, Willemotte J, Mendlewicz J. (1995): Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. *Int. Clin. Psychopharmacol.* **10**, 3-9
851. Van Reeth O, Olivares E, Zhang Y, Tripathi B, Turek FW. (1999): Chronobiotic effects of gepirone, a potential antidepressant with 5HT1A receptor partial agonist properties. *Behav. Pharmacol.* **10**, 119-130
852. van Waarde JA and Stek ML. (2001): [Electroconvulsive therapy effective and safe in 55 patients aged 56 years and older with mood disorders and physical comorbidity]. *Ned. Tijdschr. Geneesk.* **145**, 1693-1697
853. Varney NR, Garvey MJ, Cook BL, Campbell DA, Roberts RJ. (1993): Identification of treatment-resistant depressives who respond favorably to carbamazepine. *Ann. Clin. Psychiatry* **5**, 117-122

854. Vis PM, van BM, Einarson TR. (2005): Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials. *Ann. Pharmacother.* **39**, 1798-1807
855. Volz HP and Laux P. (2000): Potential treatment for subthreshold and mild depression: a comparison of St. John's wort extracts and fluoxetine. *Compr. Psychiatry* **41**, 133-137
856. Wade AG, Toumi I, Hemels ME. (2005a): A pharmacoeconomic evaluation of escitalopram versus citalopram in the treatment of severe depression in the United Kingdom. *Clin. Ther.* **27**, 486-496
857. Wade AG, Toumi I, Hemels ME. (2005b): A probabilistic cost-effectiveness analysis of escitalopram, generic citalopram and venlafaxine as a first-line treatment of major depressive disorder in the UK. *Curr. Med. Res. Opin.* **21**, 631-642
858. Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS, Childress A, Donnelly C, Deas D. (2003): Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA* **290**, 1033-1041
859. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. (2006): A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J. Am. Acad. Child Adolesc. Psychiatry* **45**, 280-288
860. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. (2004): A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am. J. Psychiatry* **161**, 1079-1083
861. Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. (1998): Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J. Clin. Psychopharmacol.* **18**, 274-281
862. Walker R and Swartz CM. (1994): Electroconvulsive therapy during high-risk pregnancy. *Gen. Hosp. Psychiatry* **16**, 348-353
863. Wallace AE, Neily J, Weeks WB, Friedman MJ. (2006): A cumulative meta-analysis of selective serotonin reuptake inhibitors in pediatric depression: did unpublished studies influence the efficacy/safety debate? *J. Child Adolesc. Psychopharmacol.* **16**, 37-58
864. Warneke L. (1993): Managing resistant depression. When patients do not respond to therapy. *Can. Fam. Physician* **39**, 843-850
865. Wassermann EM. (1998): Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol* **108**,
866. Ween JE. (2005): Prophylactic mirtazapine may help to prevent post-stroke depression in people with good cognitive function. *Evid. Based. Ment. Health* **8**, 74

867. Weihs KL, Settle EC, Jr., Batey SR, Houser TL, Donahue RM, Ascher JA. (2000): Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J. Clin. Psychiatry* **61**, 196-202
868. Weinrieb RM, Auriacombe M, Lynch KG, Lewis JD. (2005): Selective serotonin reuptake inhibitors and the risk of bleeding. *Expert. Opin. Drug Saf* **4**, 337-344
869. Weintraub D, Morales KH, Moberg PJ, Bilker WB, Balderston C, Duda JE, Katz IR, Stern MB. (2005): Antidepressant studies in Parkinson's disease: a review and meta-analysis. *Mov Disord.* **20**, 1161-1169
870. Weissman, M.M., Markowitz, J.C. & Klerman, G.L. (2000): Comprehensive Guide to Interpersonal Psychotherapy. New York
871. Wen SW, Yang Q, Garner P, Fraser W, Olatunbosun O, Nimrod C, Walker M. (2006): Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. *Am. J. Obstet. Gynecol.* **194**, 961-966
872. Wharton RN, Perel JM, Dayton PG, Malitz S. (1971): A potential clinical use for methylphenidate with tricyclic antidepressants. *Am. J. Psychiatry.* **127**, 1619-1625
873. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. (2004): Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* **363**, 1341-1345
874. WHO. (2005): WHO Resource Book on Mental Health, Human Rights and Legislation.
875. Wichers M and Maes M. (2002): The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. *Int. J. Neuropsychopharmacol.* **5**, 375-388
876. Wilcox CS, Ferguson JM, Dale JL, Heiser JF. (1996): A double-blind trial of low- and high-dose ranges of gepirone-ER compared with placebo in the treatment of depressed outpatients. *Psychopharmacol. Bull.* **32**, 335-342
877. Wilde MI and Benfield P. (1995): Tianeptine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* **49**, 411-439
878. Wilson K, Mottram P, Sivanranthan A, Nightingale A. (2001): Antidepressant versus placebo for depressed elderly. *Cochrane. Database. Syst. Rev.* CD000561
879. Wingen M, Bothmer J, Langer S, Ramaekers JG. (2005): Actual driving performance and psychomotor function in healthy subjects after acute and subchronic treatment with escitalopram, mirtazapine, and placebo: a crossover trial. *J. Clin. Psychiatry* **66**, 436-443
880. Winkler D, Pjrek E, Kasper S. (2005): Anger attacks in depression--evidence for a male depressive syndrome. *Psychother. Psychosom.* **74**, 303-307
881. Wisner KL, Gelenberg AJ, Leonard H, Zarin D, Frank E. (1999): Pharmacologic treatment of depression during pregnancy. *JAMA* **282**, 1264-1269

882. Wisner KL, Zarin DA, Holmboe ES, Appelbaum PS, Gelenberg AJ, Leonard HL, Frank E. (2000): Risk-benefit decision making for treatment of depression during pregnancy. *Am. J. Psychiatry* **157**, 1933-1940
883. Wittchen HU. (1994): Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr. Res.* **28**, 57-84
884. Wittchen HU and Pittrow D. (2002): Prevalence, recognition and management of depression in primary care in Germany: the Depression 2000 study. *Hum. Psychopharmacol.* **17 Suppl 1:S1-11.**, S1-11
885. Woelk H. (2000): Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. *BMJ* **321**, 536-539
886. Wohlfarth T, Storosum JG, Elferink AJ, van Zwieten BJ, Fouwels A, van den BW. (2004): Response to tricyclic antidepressants: independent of gender? *Am. J. Psychiatry.* **161**, 370-372
887. Wohlfarth TD, van Zwieten BJ, Lekkerkerker FJ, Gispen-de Wied CC, Ruis JR, Elferink AJ, Storosum JG. (2006): Antidepressants use in children and adolescents and the risk of suicide. *Eur. Neuropsychopharmacol.* **16**, 79-83
888. Wolkowitz OM, Reus VI, Chan T, Manfredi F, Raum W, Johnson R, Canick J. (1999a): Antigluco-corticoid treatment of depression: double-blind ketoconazole. *Biol. Psychiatry* **45**, 1070-1074
889. Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E. (1999b): Double-blind treatment of major depression with dehydroepiandrosterone. *Am. J. Psychiatry* **156**, 646-649
890. Wolkowitz OM, Reus VI, Manfredi F, Ingbar J, Brizendine L, Weingartner H. (1993): Ketoconazole administration in hypercortisolemic depression. *Am. J. Psychiatry* **150**, 810-812
891. Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, Ormiston S, Johnson R, Canick J, Brizendine L, Weingartner H. (1997): Dehydroepiandrosterone (DHEA) treatment of depression. *Biol. Psychiatry* **41**, 311-318
892. Wong AH, Smith M, Boon HS. (1998): Herbal remedies in psychiatric practice. *Arch. Gen. Psychiatry* **55**, 1033-1044
893. Wong ML and Licinio J. (2004b): From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nat. Rev. Drug Discov.* **3**, 136-151
894. Wong ML and Licinio J. (2004a): From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nat. Rev. Drug Discov.* **3**, 136-151
895. Woods SW and Rizzo JA. (1997): Cost-effectiveness of antidepressant treatment reassessed. *Br. J Psychiatry.* **170:257-63.**, 257-263
896. Workman EA and Short DD. (1993): Atypical antidepressants versus imipramine in the treatment of major depression: a meta-analysis. *J. Clin. Psychiatry* **54**, 5-12

897. World Health Organization. (1992): The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland
898. World Health Organization. The Global Burden of Disease Project. (2002). Ref Type: Internet Communication
899. World Health Organization. Depression. (2005a)WHO report on mental health http://www.who.int/mental_health/management/depression/definition/en/. Ref Type: Electronic Citation
900. World Health Organization. WHO Model List of Essential Medicines. (2005b)(7-3-2006b). Ref Type: Internet Communication
901. Wu JC and Bunney WE. (1990): The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am. J. Psychiatry* **147**, 14-21
902. Wulsin LR and Singal BM. (2003): Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom. Med.* **65**, 201-210
903. Xia Z, DePierre JW, Nassberger L. (1996): Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacology* **34**, 27-37
904. Yang X, Liu X, Luo H, Jia Y. (1994): Clinical observation on needling extrachannel points in treating mental depression. *J Tradit. Chin Med.* **14**, 14-18
905. Yatham LN. (2005): Atypical antipsychotics for bipolar disorder. *Psychiatr. Clin. North Am.* **28**, 325-347
906. Yerevanian BI, Koek RJ, Feusner JD, Hwang S, Mintz J. (2004): Antidepressants and suicidal behaviour in unipolar depression. *Acta Psychiatr. Scand.* **110**, 452-458
907. Yonkers KA and Brawman-Mintzer O. (2002): The pharmacologic treatment of depression: is gender a critical factor? *J Clin Psychiatry.* **63**, 610-615
908. Zanardi R, Serretti A, Rossini D, Franchini L, Cusin C, Lattuada E, Dotoli D, Smeraldi E. (2001): Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. *Biol. Psychiatry* **50**, 323-330
909. Zanardi R and Smeraldi E. (2005): A double-blind, randomised, controlled clinical trial of acetyl-L-carnitine vs. amisulpride in the treatment of dysthymia. *Eur. Neuropsychopharmacol.*
910. Zarate CA, Jr., Tohen M, Baraibar G. (1997): Combined valproate or carbamazepine and electroconvulsive therapy. *Ann. Clin. Psychiatry* **9**, 19-25
911. Zhang W, Perry KW, Wong DT, Potts BD, Bao J, Tollefson GD, Bymaster FP. (2000): Synergistic effects of olanzapine and other antipsychotic agents in

- combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. *Neuropsychopharmacology*. **23**, 250-262
912. Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Attiullah N, Boerescu D. (2006): How Should Remission From Depression Be Defined? The Depressed Patient's Perspective. *Am. J Psychiatry*. **163**, 148-150
913. Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. (2000): Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J. Psychiatr. Res.* **34**, 171-181
914. Zobel AW, Yassouridis A, Frieboes R-M, Holsboer F. (1999): Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. *Am. J. Psychiatry* **156**, 949-951
915. Zullino D and Baumann P. (2001): Lithium augmentation in depressive patients not responding to selective serotonin reuptake inhibitors. *Pharmacopsychiatry* **34**, 119-127

18 Annexes

18.1 Annex 1 - Additional information on the types of economic evaluation

18.1.1 Cost-offset studies

The simplest of economic studies are concerned only with costs, not (usually) because they see outcomes as irrelevant but because, in relation to the treatments or services under study, the health and quality of life outcomes have already been established from other research, or are (currently) not measurable because of conceptual difficulties or research funding limitations. One of these cost-only methods is the cost-offset study, which compares costs incurred with (other) costs saved. For instance, a new antidepressant may have a higher acquisition cost (higher price) compared to an older drug, but may reduce the need for in-patient admissions and thus lead to cost savings downstream.

While a cost-offset study is not an economic evaluation, and therefore cannot answer the ‘Is it worth it?’ question, it nevertheless addresses an issue that is often fundamental to health system decision-making: Within a fixed or even shrinking budget (at least in the short run), are treatment changes affordable?

18.1.2 Cost-effectiveness analysis

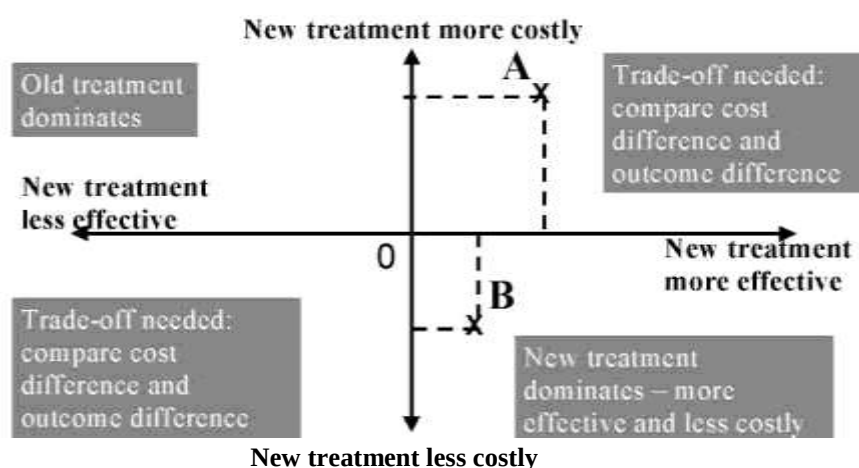
Probably the most intuitive and straightforward modes of economic evaluation are cost-effectiveness and cost-consequences analyses. Both types of analysis measure outcomes using instruments and scales familiar to clinical researchers. Both are employed to help decision makers choose between alternative interventions available to or aimed at specific patient groups. A cost-effectiveness analysis (CEA) looks at a single outcome dimension - such as the number of life years saved, the number of depression-free days or the duration of time in remission - and then computes and compares the ratio of the difference in costs between the

two treatments being evaluated to the difference in (primary) outcome (the incremental cost-effectiveness ratio or ICER).

A common finding is that a new treatment is both more effective (the outcome profiles are better than for the older or comparator treatment) and simultaneously more expensive. Decision makers therefore face the challenge of weighing up the outcomes against the higher expenditure necessary to secure them. The decision is far from straightforward in these cases. The widely used cost-effectiveness 'plane' (Figure 5) illustrates the range of possible CEA results and the difficult decision making task in some circumstances.

Figure 5

Cost-effectiveness of antidepressant treatment (from (Woods et al., 1997))



The cost-effectiveness plane in Figure 5 shows the possible combinations of outcomes and costs when comparing two interventions or treatments. The point marked as B indicates that the new treatment (say a new antidepressant drug) is both more effective (it has better outcomes) and less costly than the old treatment. The task for the decision maker looks quite straightforward in these circumstances: recommend wider use of the new treatment. However, many evaluations find that new treatment modes produce better outcomes than older interventions but at a higher cost (illustrated by point A). The choice facing the decision maker is now more complex: are the better outcomes worth the higher costs?

To aid such decision making, economists have developed cost-utility analysis (see below) and more recently the net benefit approach, linked to the construction of cost-effectiveness acceptability curves (CEACs). These show the probability that a new intervention will be reviewed by the decision maker as cost-effective for each pre-specified or implicit valuation of an outcome improvement. Comparisons are then possible across quite disparate clinical areas (comparing, for example, depression treatment with dementia treatment; or psychiatry with oncology). This kind of decision context is exactly the one faced by decision makers one or two steps removed from the patient interface.

An obvious weakness with the strict cost-effectiveness methodology is the enforced focus on a single outcome dimension (in order to compute ratios) when we know that many people with depression have multiple needs for support and when most clinicians might expect to achieve improvements in meeting more than one need. Carrying multiple outcomes forward in an analysis is less tractable analytically, but three options are available, associated with three other modes of economic evaluation. One option - which is cost-consequences analysis - is to retain all or most outcome dimensions (measured using standard clinical scales). The other two options weight the outcomes, either in terms of money (cost-benefit) or in terms of utility (cost-utility).

A weakness noted earlier is that the comparator in a trial may not be appropriate, not giving decision makers the evidence base they need (in their local circumstances, or more generally).

18.1.3 Cost-utility analysis

An increasingly used evaluative mode that seeks to reduce outcomes to a single dimension is cost-utility analysis (CUA), which measures and then values the impact of an intervention in terms of improvements in preference-weighted, health-related quality of life. The value of the quality of life improvement is measured in units of 'utility', usually expressed by a combined index of the mortality and quality of life effects of an intervention. The best-known and most

robust index is the Quality Adjusted Life Year (QALY). CUAs have a number of distinct advantages, including using a unidimensional measure of impact, a generic measure which allows comparisons to be made across diagnostic or clinical groups (for example, comparing psychiatry with oncology or cardiology), and a fully explicit methodology for weighting preferences and valuing health states. But these same features are sometimes seen as disadvantages: the utility measure may be too reductionist, the generic quality of life indicator may be insufficiently sensitive to the kinds of change expected in depression treatment, and a transparent approach to scale construction paradoxically opens the approach to criticism from those who question the values thereby obtained (Chisholm et al., 1997). On the other hand, CUAs avoid the potential ambiguities with multi-dimensional outcomes in cost-consequences studies and are obviously more general than the single-outcome CEA. The transparency of approach is also to be welcomed. The result is an incremental cost-utility ratio for each intervention, relative to some comparator, which can be compared with similar ratios for other interventions (potentially from across the widest diagnostic range i.e. not just from mental health). These cost-per-QALY ratios can then inform health care resource allocation decisions or priority setting.

18.1.4 Cost-benefit analysis

Cost-benefit analysis (CBA) asks whether a treatment or policy is socially worthwhile in the broadest sense: Do the benefits exceed the costs? This kind of analysis would allow decision makers to consider the merits not only of allocating resources within health care, but also to consider whether it would be more appropriate to invest in other sectors such as housing, education or even the military. All costs and benefits are valued in the same (monetary) units. If benefits exceed costs, the evaluation would recommend providing the treatment, and vice versa. With two or more alternatives, the treatment with the greatest net benefit would be deemed the most efficient. CBAs are thus intrinsically attractive, but conducting them is

especially problematic because of the difficulties associated with valuing outcomes in monetary terms.

Recent methodological advances in health economics offer ways to obtain direct valuations of health outcomes by patients, relatives or the general public. These techniques ask individuals to state the amount they would be prepared to pay (hypothetically) to achieve a given health state or health gain, or observe actual behavior and impute the implicit values. However, they are likely to be quite difficult to apply in mental health contexts. Another approach used to value health interventions is 'conjoint analysis'. Individuals are asked to rank different real world scenarios, which may consist of several dimensions (including, for instance, health outcomes, time inputs, discomfort, possible externalities and stigma) and by including cost as one of these dimensions a monetary value can be elicited. While complex, this conjoint analysis approach has the advantage of not specifically asking individuals to put a monetary value on health states or health gain, which can make the technique easier to administer than traditional willingness to pay studies.

18.1.5 Cost-consequences analysis

A cost-consequences analysis has the ability to evaluate policies and practices in a way that arguably comes quite close to everyday reality, but it also has some limitations. For each treatment alternative a cost-consequences evaluation computes total (and component) costs and measures change along every one of the relevant outcome dimensions. The cost and outcome results are then reviewed by decision makers, the different outcomes weighed up (informally and subjectively) and compared with costs. For example, the researcher could compute a series of ICERs (one for each measured outcome) for presentation to the decision maker. The decision calculus is therefore certainly much less tidy and more complicated than when using cost-effectiveness ratios or monetary or utility measures of impact (see below), but it could be argued that decision-makers in health care systems - from strategic policy-

makers at macro level to individual psychiatrists at micro level - face these kinds of decisions daily.

On the other hand, the process of weighing up the various outcomes by the decision maker of is subjective, hidden and 'technocratic', whereas the choice of the single outcome dimension in a CEA and the weighting algorithms in other evaluative modes (described below) are transparent, less likely to be influenced by the personal predilections or value positions of a few individuals, and (potentially) reflective of societal values.

18.1.6 Cost-minimization analysis

Another 'cost-only' approach is cost-minimization analysis, which seeks to find which of a number of treatment options has the lowest cost. A cost-minimization analysis is carried out in one of two ways. It often proceeds in the knowledge that previous research has shown outcomes to be identical in the treatment or policy alternatives being evaluated. In this sense the approach is really more accurately described as an 'interrupted' cost-effectiveness analysis (see below). The other way a cost-minimization analysis can proceed is to compare costs without any regard for outcomes. Such an approach is narrow and potentially misleading and should never be encouraged: it is not an economic evaluation.

Well-conducted cost-minimization analysis can therefore be thought of as a special type of cost-effectiveness analysis, where evidence on effectiveness demonstrates no difference between two or more interventions. In most instances, however, clinical and quality of life outcomes will not be equivalent, and more complex evaluations are required, which can make them far more informative, but correspondingly more complex to conduct.

18.2 Annex 2 - Additional information on Electroconvulsive Therapy

Electroconvulsive therapy is the safe induction of a series of generalized epileptic seizures for therapeutic purposes using brief-pulse stimulation techniques under anesthesia and muscle relaxation. Informed consent of the patient or the responsible legal guardian is mandatory. Since the first publication of a placebo controlled double-blind study indicating the efficacy of ECT in the treatment of depression (Greenblatt et al., 1964) the excellent therapeutic effectiveness of this method has been described in extensive studies (Abrams, 2002; Baghai et al., 2005) which are summarized in a recent review (ECT review group, 2003).

18.2.1 ECT as first line treatment

In case of refusal of food and drinking and severe psychomotor retardation ECT has shown to be one of the safest therapeutic options with the fastest relief of symptoms (Gangadhar et al., 1982). Therefore depressive stupor and inanition as in melancholic and/or psychotic depression can be a first line indication for ECT before other treatments are prescribed. If due to other conditions, e.g. severe psychotic symptoms and/or high suicide risk, a rapid improvement is crucial for the patient ECT should be considered earlier than other therapeutic options (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In psychotic depression, the remission rate for ECT approximates 90%, with relief experienced within 10 to 14 days (Ottoson et al., 2004; Petrides et al., 2001). The risks of suicide that mark severe psychiatric illnesses are quickly relieved by ECT, although attention to continuation treatments is essential to sustain the benefit (Kellner et al., 2005). Also other acute psychiatric syndromes such as severe excitement e.g. in delirious mania and malignant catatonia that mark systemic illnesses as lupus erythematosus, a neuroleptic malignant syndrome and medication toxicity may require ECT as a first line treatment (Abrams, 2002; Baghai et al., 2005). Intensive ECT, usually administered daily (en bloc), relieves the high

rates of mortality associated with malignant catatonia and delirious mania (Fink, 1999; Fink et al., 2003). In addition, when depression, mania, and psychotic symptoms accompany systemic illnesses or are present during early pregnancy or the post-partum breast-feeding period, the administration of medications are often precluded and ECT becomes a useful treatment option. In the case of severe and life threatening adverse events of antidepressants and in psychotic depressed patients also in case of severe adverse events due to neuroleptics, ECT monotherapy can be a safe first-line treatment. This is also true for patients suffering from severe somatic diseases including the risk of worsening due to antidepressant and antipsychotic pharmacotherapy (Beliles et al., 1998; Franco-Bronson, 1996; Rothschild, 1996). In addition due to both, a long duration and a chronic course of the index episode are negative outcome predictors in depressive disorders concerning a higher risk for therapy resistance against medication and ECT (Beliles et al., 1998; Prudic et al., 1990), more patients than today should be informed about these possible response rates to be involved properly in a shared decision making concerning their antidepressant treatment. Nevertheless the primary use of ECT is handicapped by the severe stigma and even legal restrictions against its use in some jurisdictions (Ottoson et al., 2004). A barrier to this use of ECT is the requirement for individual signed consent, a requirement that is not necessary in the prescription of other treatments for these conditions. Patients in stupor, manic excitement, catatonic mutism, and acute paranoid states may not be able to offer written consent and alternative consent processes which vary with jurisdictions in different countries must be applied as described before. It is useful for practitioners, who are responsible for the more acute and severely ill psychiatric patients, to consider ECT as a primary indication and to be acquainted with all the means for proper consent for treatment within their jurisdiction.

18.2.2 ECT as second line treatment

Even if patients receive ECT only in rare cases immediately after reaching criteria for pharmacotherapy resistance, those treatment failures are the most frequent ECT indication (Möller, 1997; Prudic et al., 1996; Sackeim, 2001; Warneke, 1993). The utilization of ECT enhances response rates significantly (Davidson et al., 1978; Folkerts et al., 1997; Kroessler, 1985). This is especially true in patients suffering from psychotic depression, even if antipsychotic therapies have been applied adequately (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Folkerts et al., 1997). Intolerable side effects of antidepressant medications, somatic comorbidities emerging during the pharmacological treatment (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001; Rasmussen et al., 2002) or worsening of depressive symptoms including severe suicidality during an antidepressant pharmacotherapy can be also the cause of initiating an ECT treatment course (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). First- and second-line indications and rare *last resort* indications are summarized in Table 14.

Table 14

Indications for Electroconvulsive Therapy (adopted from (Baghai et al., 2005))

Category of ECT-Indications Indication

ECT as a first-line treatment		<ul style="list-style-type: none"> • catatonia* • malignant neuroleptic syndrome* • severe depressive episode** • schizoaffective psychosis** • schizophrenia**, *** • in case of life threatening or intolerable side effects of psychopharmacological treatments
ECT as a second-line treatment	medication treatment failures in: depression	<ul style="list-style-type: none"> • schizoaffective psychosis • schizophrenia • mania • depression or psychotic symptoms in case of organic diseases
ECT as a last resort treatment	treatment resistant obsessive compulsive disorder (OCD) treatment resistant dyskinesias	<ul style="list-style-type: none"> • treatment resistant Gilles de la Tourette-syndrome • treatment resistant epilepsy • Parkinson's disease (treatment resistant) • protected wards, psychotic symptoms or
* (Fink et al., 2003)		
** with suicidality which can not be handled even on depressive		
stupor, with positive symptoms or acute danger of self harm or harm of others		
*** (Fink et al., 1996b)		

18.2.3 Efficacy of ECT depressive syndromes of differential etiology

18.2.3.1 Unipolar depression

The general efficacy and superiority of ECT in comparison to antidepressant pharmacotherapy has been described in controlled clinical trials and meta analyses (ECT review group, 2003). Response rates between 80-90% (Prudic et al., 1990; Prudic et al., 1996) and even 100% (Sackeim et al., 2000) have been reported. Also lower response of about 50-60% rates have been described in patients after several medication treatment failures receiving unilateral ECT (Sackeim et al., 2000). Nevertheless in a recent study sustained response rates of 80%, superior to pharmacotherapy response rates (up to 70%), and remission rates of 75% (up to 87% for study completers suffering from psychotic depression) have been found in major

depressed patients treated with optimized ECT (Husain et al., 2004; Kellner et al., 2005; O'Connor et al., 2001; Petrides et al., 2001).

A 20% better improvement in comparison to tricyclic antidepressants and a 45% better improvement in comparison to MAOI (Janicak et al., 1985) as well as a better improvement in comparison to the SSRI paroxetine (Folkerts et al., 1997) have been described. In addition, a more rapid improvement in comparison to pharmacotherapeutic approaches has been published (Abrams, 2002; Petrides et al., 2001; Prudic et al., 1996; Sackeim et al., 1993). Most patients show a faster treatment response during ECT in comparison to pharmacotherapy (Sackeim et al., 1987). But also an advantage concerning speed of response in similar efficacious pharmacotherapeutic approaches such as lithium augmentation (Sackeim et al., 1993) after TCA treatment failures have been described. Especially in patients receiving ECT after pharmacotherapy treatment failures, longer treatment intervals until complete remission have to be expected.

In former publications using lower stimulation energy bilateral ECT has been shown to be more effective than unilateral ECT (ECT review group, 2003; Sackeim et al., 1987; Sackeim et al., 1993). In addition, unilateral ECT may achieve efficacy rates equal to bilateral ECT if the dose regime is 6-8x above the titrated seizure threshold (McCall et al., 2000; Sackeim et al., 2000). In this case the requirement of a calibration session, probably ineffective for antidepressant treatment, can slow down the decrease of depressive symptoms. In addition cognitive adverse events are identical to those of bilateral ECT.

18.2.3.2 Bipolar depression

ECT is an effective antidepressant therapy regardless if depressive episodes occur due to MDD or bipolar disorder (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). As described in chapter 5.2.2 an enhanced switch-risk including the occurrence of hypomania or mania can be observed during every highly

effective antidepressant treatment. Infrequent switches from depression to mania may also occur during the course of ECT (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001), but due to missing randomized controlled trials and switch rates up to 30% regardless of antidepressant therapies this clinical observation also has been discussed as an artifact (Taylor et al., 2006). On the contrary to antidepressant pharmacotherapy, the treatment has not to be stopped due to the anti-manic properties of ECT. Furthermore ECT may be combined with lithium treatment to augment lithium effects and to prevent the switch into mania in high-risk patients. In this case an enhanced risk for cognitive and medical side effects has to be taken into account (Zarate, Jr. et al., 1997). Even a combined use of ECT and anticonvulsants in case of urgent indications of mood stabilizers is possible and may yield clinical advantages (Aarre et al., 2002; Pearlman et al., 1995; Zarate, Jr. et al., 1997).

18.2.3.3 Dysthymia and double depression

Chronic depression in case of dysthymia alone is not an indication for ECT treatment. Nevertheless if the diagnostic criteria for MDD or double depression are present, dysthymia is not a predictor for a poor ECT response (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

18.2.3.4 Depressive syndromes in obsessive compulsive disorder (OCD)

In patients suffering from OCD not responsive to pharmacotherapy, response after ECT may be expected if OCD is accompanied by depressive symptoms (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001), which often is the case. Also the beneficial use of ECT during OCD continuation therapy has been reported (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001).

18.2.3.5 Comorbid personality disorder

Comorbid personality disorder is a predictor of poor response to ECT and the recommendation for ECT should be cautious in such patients (Abrams, 2002; O'Connor et al., 2001). Nevertheless ECT should not be kept back from patients suffering from MDD with comorbid personality disorders in case of pharmacotherapy resistance (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). The information about lower response rates has to be included in the patient information about the estimated treatment outcome.

18.2.3.6 Organic depression due to somatic disorders

Patients suffering from secondary depression associated with somatic diseases show lower response rates to biological therapies such as pharmacotherapy or ECT (Black et al., 1993; Coryell et al., 1985; Krystal et al., 1997) in comparison to MDD. Nevertheless ECT is clinically effective in patients suffering from depression after cerebral infarction ("poststroke depression") (Krystal et al., 1997; Sackeim et al., 1987; Sackeim et al., 2000). But of course especially in this patient group organic risk factors have to be considered thoroughly during interdisciplinary neurologic and psychiatric evaluations.

18.2.4 Combination of ECT and antidepressants

In spite of the higher efficacy and clinical effectiveness of ECT in comparison to pharmacotherapy not all patients respond to conventional ECT monotherapy. The majority of patients referred for ECT have had multiple trials of medication. Despite this experience high remission rates to effective ECT up to 90% in psychotic depression can be expected (Abrams, 2002; Husain et al., 2004; Petrides et al., 2001). The use of bilateral or high-dose unilateral stimulation can enhance the effectiveness of ECT treatment (Husain et al., 2004; Sackeim et al., 2000). A further option to augment an ECT treatment course may be the concomitant

prescription of antidepressants. However study results on a putative benefit combining ECT with TCA (Lauritzen et al., 1996; Nelson et al., 1989) and the lack of advantages of other concomitant medication like SSRI are still controversial (Lauritzen et al., 1996). Especially the efficacy of modern antidepressants in combination with ECT, e.g. the dually acting substances mirtazapine and venlafaxine, has never been investigated in controlled studies. Nevertheless some safety data are available, e.g. venlafaxine at dosages lower than 300mg/day has been shown to be safe in combination with ECT. In high dose treatments above 300mg/d side effects of cardiovascular nature such as transient asystolia or bradycardia were more frequent if venlafaxine treatment was combined with propofol anesthesia during ECT (Lauritzen et al., 1996).

Due to the severity of depressive syndromes in patients after medication treatment failures, the clinical recommendation therefore is to combine ECT with antidepressants at moderate doses during the whole treatment course or at least during the last two weeks of ECT treatment to prevent exacerbation of depression after ECT during the usual latency until antidepressant response is achieved after initiating pharmacotherapy.

18.2.5 Continuation ECT (C-ECT)¹⁹

As described in chapters 12 and 12.2 besides pharmacologic and psychotherapeutic continuation therapies especially after pharmacotherapy treatment failures, also ECT is an effective continuation treatment (Fink et al., 1996a; Kellner et al., 2005; Sartorius et al., 2005a; Sartorius et al., 2005b), even if the scientific evidence for use of ECT as a maintenance treatment is limited due to an absence of controlled studies. Continuation ECT should be considered in cases of recurrence of depressive symptoms despite adequate pharmacologic

¹⁹ The terms *continuation treatment* and continuation ECT (C-ECT) are predominantly used to characterize the maintenance treatment after successful treatment of the index phase. It is sometimes distinguished from *maintenance treatment* and maintenance ECT (M-ECT) (Sartorius et al., 2005a) due to theoretical considerations about a switch to prophylactic treatment preventing new episodes of depression. Because this time point cannot be defined precisely in an individual patient, in the following text only the term C-ECT is used.

continuation therapy. Even if the prior history of an individual patient shows an enhanced risk for recurrence of depression during continued pharmacotherapy including both antidepressants and mood stabilizers, C-ECT should be part of the treatment plan (Frey et al., 2001; McCall, 2001; Rabheru et al., 1997). The usual clinical procedure is to prolong the treatment intervals according individual clinical requirements. During the acute treatment a patient usually receives two or three treatment per week. Afterwards usually one treatment per week is applied for four to eight weeks, then one treatment every two weeks and one treatment every four weeks. This frequency should be maintained for at least six months. A frequently used alternative strategy (the so called *cafeteria style*) is the individual decision, whether an C-ECT treatment is administered when the first signs of recurrence of depressive symptoms are reported (Abrams, 2002; Fink et al., 1996a). Regular weekly evaluations help to judge about the necessity to shorten the treatment free intervals on an individual basis. The same evaluation is necessary during the attempt to stop ECT treatment after six month. As soon as depressive symptoms reoccur, a prolongation of the C-ECT should be applied.

18.2.6 Safety

In general ECT is one of the best tolerated antidepressant therapies with low risk for severe complications, even lower than during the application of TCA (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). The mortality rate during ECT varies between 1 : 50,000 and 1 : 25,000 treatments (Abrams, 2002; American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). In less than one in 10,000 treatments severe complications are seen that warrant special attention (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). ECT therefore is considered to be one of the safest medical procedures under anesthesia. Clinical conditions requiring special attention before and during an ECT described in (Abrams, 2002; Baghai et al., 2005) are summarized in Table 15.

Table 15

Clinical conditions requiring special attention before and during ECT (adopted from (Baghai et al., 2005))

Category Enhanced	Clinical condition
intracerebral pressure*	at present
Cerebral infarction*	not older than 3 month
Myocardial infarction*	not older than 3 month
Intracerebral tumor*	including intracerebral edema
Any life threatening anesthesia risk*	at present
Cardiovascular disorders	cardiac arrhythmias, instable angina pectoris, myocardial infarction (older than 3 month), myocardial insufficiency, heart valve abnormalities, not sufficiently treated hyper-or hypotonia, aortal aneurysm
Medical disorders Neurological disorders	disturbance of blood coagulation, severe liver diseases, severe pulmonal diseases, pheochromocytom
Orthopedic disorders Esophageal hernia	intracerebral neoplasias, intracranial bleeding, intracerebral vascular malformations, cerebral ischemia, cerebral inflammations, hydrocephalus, dementias, diseases of the basal ganglia, craniotomies, severe cerebral traumas
Concomitant pharmacological treatment	osteoporosis
* bold: in former times considered as absolute contraindications; today an individual risk/benefit-analysis is necessary.	increased aspiration risk; intubation recommended
	if enhancing the ECT risks or reducing ECT efficacy

18.2.7 Side effects

18.2.7.1 Somatic side effects

The most frequent immediate unpleasant effects of ECT are headache, nausea and vomiting (varying with anesthetic). In up to 45% patients report headache which can be treated symptomatically using analgesics such as acetylsalicylic acid or paracetamol and if severe, by changing the induction medications.. Patients suffering from regular migraine attacks are predisposed for postictal headache after ECT. In this case triptans, e.g. sumatriptan can be applied orally or intranasal (Angst et al., 1992). Nausea occurs rarely after i.v. anesthesia and can be treated using metoclopramide. Other rare complications of ECT can be cardiovascular

events emerging from anesthesia. On rare occasions, the seizure is prolonged beyond the anticipated 30 to 180 seconds (American Psychiatric Association Committee on Electroconvulsive Therapy et al., 2001). This risk is considerably enhanced in patients receiving theophylline (Grogan et al., 1995; Rao et al., 1993). The treating anesthesiologist or psychiatrist will end the seizure by the administration of intravenous benzodiazepines (e.g. diazepam), anesthetics or other anticonvulsants. This event is best managed by ictal and postictal EEG monitoring (Grogan et al., 1995), which can be of use also in the treatment of nonconvulsive seizures which rarely occur after ECT (Grogan et al., 1995; Rao et al., 1993). In case of prolonged effectiveness of muscle relaxants due to predisposition or Lithium therapy (Hill et al., 1977; Reimherr et al., 1977) longer assisted respiration and subsequent measurement of oxygen saturation using finger or toe pulse oxymetry is necessary to prevent hypoxia. Aching muscles are prevented by adequate muscle relaxation and were reported rarely.

In patients suffering from bipolar depression ECT like any other antidepressant agent (Angst et al., 1992) can induce hypomania or mania ("switch") (Angst et al., 1992). Concomitant lithium therapy (Zarate, Jr. et al., 1997) can be used despite the higher risk of side effects such as prolonged muscle relaxation and confusional states. The use of mood stabilizers such as valproate or carbamazepine is possible despite the anticonvulsant properties of these agents (Zarate, Jr. et al., 1997). Both methods can reduce the switch-risk significantly.

18.2.7.2 Cognitive side effects

All patients are confused on awakening after a seizure. The duration and the severity of the post-seizure delirium vary with patient age (older patients have more severe and more prolonged periods of confusion), dosage and type of anesthetic, and the characteristics of the medications, both psychoactive and systemic, which may be prescribed for the patients.

Special attention is paid to sedatives and anxiolytics, antipsychotics, and lithium that may augment the confusional syndrome.

Typical side effects which are more prominent in bilateral than in unilateral and in high-dose than in lower dose ECT (ECT review group, 2003) are transient cognitive disturbances. These include short term memory disturbances in up to 30% of the treated patients (van Waarde et al., 2001). Postictal delirium including a prolonged reorientation period and memory disturbances including anterograde or retrograde amnesia can be differentiated from rarely occurring effects on the autobiographic long term memory (Lisanby et al., 2000). In addition cognitive deficits not emerging from memory disturbances, such as concentration or attention deficits can occur. It can be difficult in an individual patient to differentiate cognitive side effects of an ECT treatment from cognitive disturbances caused by depression itself (Lisanby et al., 2003a). Therefore a variety of patients report about amelioration of cognitive impairment after an ECT treatment course (Devanand et al., 1991).

As described the rate of cognitive disturbances is dependent on dose and application of electrical stimulation (Devanand et al., 1991; Krystal et al., 1997). Sometimes patients experience profound and sustained memory loss, sufficient to interfere with their ability to return to work. Such instances are extremely rare but are the principal burden of the complaints against the use of ECT (Abrams, 2002; Ottoson et al., 2004). Nevertheless recent improvements in the use of ECT include methods to maintain the good therapeutic efficacy together with a better tolerability concerning cognitive disturbances. Using modified ECT techniques (Ghaziuddin et al., 2000) including unilateral or bifrontal pulse wave stimulation, anesthesia with muscle relaxation and sufficient oxygenation these risks could be reduced substantially (Ghaziuddin et al., 2000; Sackeim et al., 1993; Sackeim et al., 2000).

If in spite of these precautions cognitive disturbances occur, a rapid improvement within one and up to four weeks can be observed in most cases (Ghaziuddin et al., 2000). Follow-up

investigations showed a complete reversibility of cognitive side effects after an ECT course (Ghaziuddin et al., 2000; Krause et al., 1988) or even an improvement in comparison to the time interval before ECT treatment (Baghai et al., 2005; Krause et al., 1988). A variety of case reports, case series and controlled studies confirm that ECT does not cause long lasting functional (Krause et al., 1988) or any structural damage of the central nervous system (Devanand et al., 1991; Krause et al., 1988; Lisanby et al., 2003b).

18.2.8 Clinical precautions and special considerations

After many decades of research and clinical experience, clinicians have developed protocols for the safe treatment of patients warranting ECT regardless of age, medical status, or physical state. No absolute contraindications are acknowledged.

Conditions including higher somatic risks are a recent myocardial or cerebral infarction, high intracranial pressure, and every untreated severe medical and life threatening anesthesiological risk. If treated sufficiently these conditions become relative contraindications and it has to be performed an individual and interdisciplinary benefit / risk analysis for each patient. Other conditions including enhanced cardiovascular risks can be coronary artery disease, arrhythmias, insufficiently treated hypertonia, or aneurysms. Other medical conditions such as severe lung or liver diseases, disturbances of blood coagulation or an untreated pheochromocytom can enhance the ECT and anesthesia risk. Neurological diseases such as intracranial tumors or bleeding, vascular malformations, cerebral ischemia, acute infections and others enhance the treatment risk. In general each factor enhancing the risk for ECT or anesthesia side effects should be taken into consideration. In case of those specific risks interdisciplinary counseling may be necessary. Afterwards the higher somatic risk has to be compared to the risk of an insufficiently treated or prolonged psychiatric illness. Patients and relatives or responsible legal guardians have to be informed about risk / benefit ratios to contribute to a shared decision.

18.3 Annex 3 - Additional information on transcranial magnetic stimulation

Transcranial Magnetic Stimulation (TMS) has been originally introduced in 1985 by Barker et al. as a non-invasive tool to electromagnetically stimulate the primary motor cortex in humans (Lisanby et al., 2003b). More recently, rTMS has become a powerful research tool in neurophysiology and cognitive neuroscience. rTMS is usually targeted to the dorsolateral prefrontal cortex based on well-replicated findings showing reversible functional changes in this region using different neuroimaging techniques. In the majority of studies the left prefrontal cortex has been chosen based on the observed asymmetry of prefrontal function associated with major depression (Lisanby et al., 2003b). A large number of different stimulation parameters, e.g. frequency and intensity of stimulation, have been applied in studies, and only very few studies have compared different treatment modalities (Padberg et al., 2003). The usual treatment duration has been one to four weeks of treatment and in most studies rTMS has been used as add-on intervention in addition to a stable antidepressant medication.

About 25 randomized, placebo-controlled clinical trials including about 750 patients suffering from major depressive episodes have been conducted to date investigating the safety and efficacy of rTMS as antidepressant intervention (Berman et al., 2000b; Dolberg et al., 2002; Garcia-Toro et al., 2001a; Garcia-Toro et al., 2001b; Kauffmann et al., 2004; Loo et al., 2003; Miniussi et al., 2005; Mosimann et al., 2004; Nahas et al., 2003; Padberg et al., 1999; Padberg et al., 2002; Padberg et al., 2003; Pascual-Leone et al., 1996; Rossini et al., 2005). Twenty of these trials have been conducted in parallel-design and three are cross-over studies (Burt et al., 2002; Pascual-Leone et al., 1996). In the majority of these trials significant placebo/verum differences have been observed with antidepressant effects ranging from modest to substantial. Due to the methodological limitations of many of these trials regarding rather

small sample sizes with sometimes even three treatment groups, the difficulty of controlling sham rTMS used as placebo condition, the modified double-blind designs with the person applying rTMS being aware of the condition and patient and rating psychiatrist being blinded and the short observation periods, the levels of evidence currently reached by the available data still needs improvement. Several meta-analyses have been conducted largely differing in the studies selected and the methodology of analysis used (Burt et al., 2002; Couturier, 2005; Ebmeier et al., 2006; Martin et al., 2003; Pascual-Leone et al., 1996; Schulze-Rauschenbach et al., 2005). Most of these meta-analyses support the antidepressant efficacy of rTMS, but clinical effects are found to be not very strong and the clinical significance may be questionable. rTMS has also been directly compared with ECT in five parallel design trials (Grunhaus et al., 2000; Grunhaus et al., 2003; Pridmore et al., 2000; Schulze-Rauschenbach et al., 2005). In these trials rTMS has been found to be equally effective compared to ECT in patients suffering from major depressive episodes without psychotic features, but to be inferior in psychotic depression (Grunhaus et al., 2000). Surprisingly, only one study compared different rTMS modalities to antidepressant pharmacotherapy (clomipramine), however, no meaningful interpretation of the results in terms of efficacy was possible due to small sizes of treatment groups (Lisanby et al., 2001b). Four trials have investigated the combined treatment with active rTMS plus antidepressant compared to sham rTMS plus antidepressant in order to answer the question whether rTMS may augment the effect of antidepressant medication (Lisanby et al., 2001b; Rumi et al., 2005). Only one study where rTMS was combined with amitriptyline found a significant superiority of combined active treatment (Rumi et al., 2005), whereas the other trials where SSRI and other substances were applied failed to show a significant difference between treatment groups. These results may support the idea that rTMS may be particularly effective combined with distinct neuropharmacological actions and this hypothesis should be systematically addressed by future studies. Apart from single studies and case reports little is known regarding the stability

of effects and potential maintenance treatment strategies (Pascual-Leone et al., 1996) and the largest body evidence points to transient effects after completion of rTMS treatment (Pascual-Leone et al., 1996; Schüle et al., 2003).

rTMS appears to be safe and well tolerated by patients within a range of parameters defined according to a consensus (Wassermann, 1998). Side effects comprise the risk of seizure induction which increases with higher intensity and higher frequency of stimulation as well as shorter intertrain intervals. Since safety criteria for limiting these stimulation parameters have been published no additional seizures have been reported within these limits. Side effects which are frequently observed are slight local painful stimulation artifacts on the scalp including muscle contractions in about 10-30% of the patients, transient headaches after stimulation (less than 5 %) and single cases of autonomous arousal reactions including dizziness and fainting (personal communications). Clinical contraindications include implanted devices (pacemakers), intracranial articles of ferromagnetic material, a history of epileptic seizures and brain injuries or surgery. There is only data from a case report regarding the use of rTMS in pregnancy. Particular attention should also be paid to psychiatric side effects of rTMS including the risk for switching into hypomania / manic states particularly in patients with bipolar disorder and the de novo induction of psychotic symptoms (Padberg et al., 2003; Rush et al., 2000).

In conclusion, there is considerable evidence of an antidepressant efficacy of high frequency rTMS over the left dorsolateral prefrontal cortex applied over two to four weeks and rTMS may be applied successfully as adjuvant antidepressant intervention. Patients with psychotic symptoms appear to have only a poor response to rTMS. There is no evidence that rTMS associated antidepressant effects are stable beyond the end of rTMS treatment. Thus, continuation therapy should be planned and initiated as recommended by current clinical guidelines. As the antidepressant efficacy of rTMS has still not been sufficiently proven due to methodological limitations of previous clinical trials, the results of several ongoing

placebo-controlled multicenter trials in the U.S. and in Germany are expected to clarify the role of rTMS within the range of antidepressant interventions. Further research should also focus on the early combined treatment with rTMS and antidepressant pharmacotherapy or psychotherapy and the long-term outcome of treatment.

18.4 Annex 4 - Additional information on vagus nerve stimulation (VNS)

In the 80ies and 90ies of the last century VNS was developed in animal models with regard to its putative anticonvulsant action and has been introduced into the routine treatment of therapy-resistant focal epilepsies about a decade ago including approval by the U.S. Food and Drug Administration (FDA). Theoretical considerations regarding the functional anatomy of the vagus nerve also projecting to areas of the brain relevant for generation and control of mood and emotions, but also observations of mood changes in epilepsy patients undergoing VNS, have triggered the application of VNS in depressive disorders (George et al., 2003). A Neuro-Cybernetic Processus (NCP) System is used for VNS consisting of a pulse generator implanted into the thoracic wall and subcutaneously implanted bipolar leads linked to the left vagal nerve. This system has been investigated in a series of open and controlled clinical trials following an industrial development program, and recently the data of the complete trial set have been published (George et al., 2005; Nahas et al., 2005; Rush et al., 2000; Rush et al., 2005b; Rush et al., 2005a; Sackeim et al., 2001).

The first open study (D-01) showed clinically meaningful effects over a period of two years with response rates between 42 and 45% (defined as at least 50% reduction of baseline Hamilton Rating Scale for Depression (HRSD) scores) and remission rates between 21 and 22% (Rush et al., 2000; Sackeim et al., 2001). However, all patients included in the first open study received additional antidepressant medication which also was changed over time. The promising results of this open pilot study led to a double-blind randomized placebo-controlled multicenter trial (D-02 study) including 235 patients who received either active or placebo stimulation during a ten weeks period (Rush et al., 2005a). After completion of the acute treatment period, all patients received continuous treatment and long-term data has been recently published of 205 patients after 12 months stimulation (Rush et al., 2005b). Patients of the placebo group also received active treatment during the long-term period and changes in

the concomitant treatment (medication and psychotherapy) were allowed according to clinical requirements ("treatment as usual" - TAU). The primary efficacy criteria of the acute study were the number of responders of the treatment groups. No difference between those groups was found in the acute study (15% response in the active versus 10% response in the placebo group), neither significant differences among the secondary efficacy criteria (self- and observer-ratings) were observed (Rush et al., 2005a). The negative finding in the acute study was discussed as being due to the low stimulation intensity applied in the active group (0.67 mA versus 0.96 mA in the D-01 study). To allow interpretation of the clinical meaning of the long-term data in terms of efficacy, a comparison study was initiated (D-04) including 124 patients receiving only TAU (George et al., 2005). This study had the same inclusion criteria as the D-02 study: Chronic depressive episode (duration longer than two years) or recurrent depression (> four episodes including the current episode), a HRSD baseline score >20 and non-response after two to four appropriate antidepressant medication trials. After twelve months a clinical response was found in 29.8% of the patients included in the D-02 study, whereas only 12.5% responded in the D-04 study, remission was achieved in 17.1% of the D-02 study compared to 6.7% of the D-04 study (George et al., 2005). Concerning the safety of VNS the results of the studies in epilepsy were essentially confirmed. After the acute study period of D-02 study voice alterations occurred in 55% of the patients versus 3% of the control group, cough was found to be increased in 24% versus 2% of the control group, dyspnoea in 19% versus 2% of the control group, neck pain in 16% versus less than 1% of the control group, dysphagia in 13% versus 0% of the control group, laryngismus in 11 % compared to 0 % in the control group, paraesthesia in 10% versus 3% in the control group, pharyngitis in 8% versus less than 1% in the control group (Rush et al., 2005a). During long-term treatment over one year most of these adverse events showed a clear decline, i.e. voice alterations, neck pain, dyspnoea were reduced by 30-50% and the other side effects showed an even more marked reduction (Rush et al., 2005b).

Based on the efficacy and safety data the VNS therapy system was recently approved by the U.S. FDA for the adjuvantive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. The following contraindications have been formulated: (1) history of bilateral or left cervical vagotomy, (2) simultaneous use of short wave diathermy, microwave diathermy or therapeutic ultrasound diathermy.

Despite the recent FDA approval the body of evidence that VNS exerts antidepressant effects superior to placebo is still limited and mainly based on long-term data compared to naturalistic treatment. A placebo-controlled trial is urgently needed to clarify the issues arising from the D-02 acute study and to provide more data for the efficacy of VNS in depression. Because of its invasive nature VNS should be reserved for special clinical cases where the patient's demand for this treatment is high, several other interventions have failed and a clinical benefit is likely. VNS should only be used as long as thorough medical follow-up is guaranteed.

18.5 Annex 5 - Additional information on Acupuncture

18.5.1 Efficacy

Due to the fact that the use of complementary and alternative therapies is overrepresented in patients suffering from depressive syndromes (Kessler et al., 2001), it is necessary to evaluate the actual knowledge about the main therapeutic options in this field. Acupuncture has a long history in the eastern culture and the traditional Chinese medicine describes influence of acupuncture on the balance of health and energy in the human body. Traditional acupuncture involves the insertion of needles into specific trigger points on different parts of the body. Despite a variety of published studies in this field, a recent review describes insufficient evidence to determine the efficacy of acupuncture in comparison to pharmacological antidepressant treatment (Smith et al., 2005). The cause for this uncertainty is the methodological quality of the up to now published investigations. Nevertheless some of these controlled studies are presented in the following to describe the present state of information. In a comparative randomized controlled trial 20 patients suffering from depression were treated with traditional acupuncture or the TCA amitriptyline. No significant differences between both treatment groups could be seen, but due to the relatively small number of patients, the study seems to be underpowered (Yang et al., 1994). A further study investigated electroacupuncture in comparison to amitriptyline and placebo in an analysis of two separated study parts. Therapeutic effects in both treatment groups showed no significant differences. A better therapeutic effect on anxiety and cognitive symptoms after acupuncture has been described (Allen et al., 1998). A further study compared acupuncture for depression with acupuncture for other complaints and a group of patients waiting for treatment in 34 patients. Patients receiving depression specific acupuncture showed significantly more improvement than the group receiving unspecific acupuncture, but no significant difference from the

placebo condition in waiting-list patients could be seen (Allen et al., 1998). A single blind study compared also depression specific and non-specific acupuncture with mianserin monotherapy in a total of 70 patients. Additionally applied acupuncture improved depression more than treatment with mianserin. No differences between both forms of acupuncture could be seen (Roschke et al., 2000). In addition specific acupuncture showed a greater and lasting amelioration of symptoms in women suffering from depression during pregnancy (Manber et al., 2004). Other authors describe some evidence for the clinical effectiveness of acupuncture, but mention the requirement of further studies before recommendations can be made (Gallagher et al., 2001; Manber et al., 2002). In addition it has to be stated, that not only randomized controlled trials of adequate power are required, but also detailed description of standardized procedures in acupuncture, to be able to compare different investigations. In addition adequate blinding of physicians and patients together with standardized outcome measures are necessary before clinical and scientific recommendations can be made (Smith et al., 2005).

18.5.2 Safety and tolerability

An overall good safety and tolerability of acupuncture has been described. Especially in trials comparing TCA with acupuncture the typical side effects were much less in the acupuncture groups (American Psychiatric Association, 1994). Studies comparing modern and better tolerated antidepressants are not published up to now

18.6 Annex 6 - Additional information on Psychotherapy

Empirically supported psychotherapies are potent alternatives to and augmentors in combination with antidepressant medications. Although psychotherapies have received less study than pharmacotherapies, randomized controlled studies have demonstrated the efficacy of some psychosocial interventions, acutely and as maintenance treatments, both as monotherapies and in combination with medication as antidepressant treatments. The empirically based psychotherapies, principally cognitive behavioral therapy (Beck et al., 1979), interpersonal psychotherapy (Weissman et al., 2000), and behavioral therapy (e.g., (Martell et al., 2001)), have advantages and disadvantages relative to pharmacotherapy, and differential benefits may exist among these psychotherapies for depressed patients with particular moderating factors.

Most psychotherapy outcome research has involved individual psychotherapy, although group and family therapies have received some study. Empirically validated treatments are time-limited, diagnosis-focused, and address current life problems rather than the past. Of the many forms of extant psychotherapy, only a few have received empirical assessment; the antidepressant benefits of the remainder remain unclear.

18.6.1 Psychotherapies as primary treatment for mood disorders

After decades of psychotherapists avoiding structured research, researchers in the 1970's began to conduct randomized controlled trials (RCTs) of psychotherapies for non-delusional outpatients with major depressive disorder (MDD). In addition to incorporating research paradigms from pharmacotherapy trials (e.g., random assignment, blinded independent assessment), researchers wrote manuals to define particular treatment approaches such as CBT and IPT. Treatment sessions were recorded to ensure therapist adherence to the treatment approach, which was reinforced by frequent supervision. Psychotherapies were

initially compared to waiting lists or low contact conditions, but increasingly also to active treatments, including antidepressant medication (e.g., (Elkin et al., 1989b)). These trials yielded repeated evidence of the efficacy of CBT and IPT as treatments for MDD (Hollon et al., 2002), leading to their incorporation into national and professional treatment guidelines (American Psychiatric Association, 2000; Depression Guideline Panel, 1993; Karasu et al., 1993; Roth et al., 2004). Lacking funding from an industry, psychotherapy researchers have conducted fewer trials than pharmacotherapy researchers. In general, empirically supported psychotherapies have demonstrated similar response and remission rates to pharmacotherapy for outpatients with MDD. They treat mood and demoralization more quickly than neurovegetative symptoms of depression, the reverse of the pattern seen for antidepressant medications. Beyond acute efficacy, IPT and CBT have been shown to provide prophylaxis against relapse and recurrence when prescribed as less frequently scheduled (e.g., monthly) maintenance treatments (Frank et al., 1990; Hollon et al., 2005a). Studies of CBT suggest an enduring effect even for acute psychotherapy, a lasting protective benefit not seen when pharmacotherapy is discontinued (Hollon et al., 2005c). This presumably indicates that psychotherapy provides patients with methods for handling new psychosocial problems, potential triggers of depressive episodes that arise in their lives after acute treatment ends. The empirical evidence for psychotherapy as monotherapy for chronic depression is sparser and less strong. Cognitive Behavioral Analysis System of Psychotherapy (McCullough, Jr., 2003) was as efficacious as nefazodone both acutely and as maintenance treatment in one large (N=681) study of chronic MDD; the combination of nefazodone and CBASP was superior to either monotherapy (Keller et al., 2000). This impressive finding requires replication, as it is the only CBASP trial published to date. IPT and CBT have shown less benefit than pharmacotherapy for dysthymic patients (Markowitz et al., 2005; Ravindran et al., 1999), albeit combined IPT and sertraline was cost effective relative to pharmacotherapy alone in one study (Browne et al., 2002).

18.6.2 Combination treatment with antidepressant medication and psychotherapy

Combined treatment studies often have been confounded by inadequate power, differential attrition, and other methodological difficulties. Large sample sizes are required to find differences between active monotherapies and combined treatment. Nonetheless, no research trial has shown combined treatment to be less efficacious than antidepressant monotherapy (Manning et al., 1992). Given health economics considerations, combined treatment may best be reserved for patients with chronic, highly comorbid, severe depressions, or those at high suicide risk (Hollon et al., 2005b; Rush et al., 1999).

18.6.3 Psychotherapy as adjunct to pharmacotherapy

Some depressed patients remit on antidepressant medication and require no additional treatment. Others, particularly chronically depressed patients, may improve symptomatically yet still function less than optimally, or feel unsure about social risks or career decisions. Such patients may benefit from adjunctive psychotherapy (Markowitz, 1993) to expand their social confidence or behavioral repertoire.

18.6.4 Differential therapeutics

Behavioral therapy helps patients to schedule pleasurable activities while avoiding painful ones. Cognitive therapy, usually combined with behavioral techniques, helps patients to identify cognitive distortions with depressive biases, thoughts that are unnecessarily painful, pessimistic, and which inhibit potentially valuable activity. IPT defines depression as a medical disorder and focuses on the connection between mood and social situations or life circumstances; it has been shown to build social skills. Understandably, these therapies may have differing appeals and benefits for different depressed individuals. A few RCTs have directly compared IPT and CBT (Elkin et al., 1989a; Rossello et al., 1999) or cognitive therapy and behavioral therapy (Jacobson et al., 1996). While showing non-

significant differences in outcome, these trials allowed evaluation of moderators of treatment outcome. For example, patients with poor concentration may respond better to IPT than CBT, whereas those with a paucity of social skills may fare better in CBT than IPT (Sotsky et al., 1991). Far more research of differential therapeutics is needed.

18.6.5 Comparing medications and psychotherapies

Medications work faster than psychotherapies and are easier to administer to large populations, although the therapeutic alliance is equally important for both antidepressant modalities (Krupnick et al., 1996). Empirically validated psychotherapies lack medication interactions, have low adverse effects, and little risk of inducing mania in depressed bipolar patients. They may address social stressors, such as marital pressures, that could potentially trigger future episodes. Psychotherapies have potential advantages for depressed women during pregnancy and nursing; may be better accepted by adolescents, particularly given recent concerns about serotonin reuptake inhibitors in this population; and although not well tested for depressed children, may be indicated inasmuch as medication has not shown benefit. In non-industrialized countries, such psychotherapies may be the only feasible, affordable treatments for depression (Bolton et al., 2003). Psychotherapies adapted to different cultures must address the specific needs and sensitivities of individuals in those cultures.

Psychotherapies are not intended to treat depression with psychotic features, nor as monotherapy for bipolar I disorder (Frank et al., 2005; Miklowitz et al., 2003). Some severely depressed patients may be too depleted to engage in psychotherapy effectively. Patient preference is a predictor of treatment outcome and hence deserves consideration in treatment selection.

On the basis of their performance in controlled efficacy trials, interpersonal psychotherapy, cognitive therapy, and behavioral therapy should be included in algorithms of standard treatment for depressive disorders.