Update on Psychotropic Medication Use in Renal Disease

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Renal failure is a common medical condition, and many patients have comorbid psychiatric disorders. In this review, which is intended as a resource for consultation psychiatrists, the authors discuss pharmacokinetic considerations and provide information about the use of individual psychotropic medications in patients with renal disease. Most psychotropic medications are fat soluble, easily pass the blood-brain barrier, are not dialyzable, are metabolized primarily by the liver, and are excreted mainly in bile. Consequently, the majority of these drugs can be safely used with the end-stage renal disease population. (Psychosomatics 2004; 45:34–48)

This article provides an update on the use of psychotropic medications in the context of impaired renal function. In preparing this article, we reviewed more than 200 citations, along with product safety and research information from the pharmaceutical firms that manufacture most of the new-generation antidepressants and atypical neuroleptics.[1] Psychiatric consultants need to be aware of the enormous prevalence of comorbid renal and psychiatric disorders, and they should be knowledgeable about the use of psychotropic medications in this situation.[2] In a recent survey of 133 hemodialysis patients, medication-related problems were identified in 98% of the subjects. The subjects had a mean of six comorbid illnesses (SD = 2.3), a mean of 11 different drugs (SD = 4.2) were prescribed per patient, and a total of 475 medication-related problems were detected.[3]

In the United States, there are approximately 300,000 patients with end-stage renal disease (ESRD) whose lives are maintained by peritoneal dialysis and hemodialysis.[4] The annual incidence of acute renal failure is approximately 200 per million population, and an additional 8 million individuals are estimated to have chronic renal insufficiency.[5] The psychiatric epidemiological literature has glaring limitations, e.g., studies estimating the prevalence of depression among dialysis patients have reported rates ranging from 0% to 100%.[6,7] Nevertheless, it is evident that a substantial proportion of the ESRD population has comorbid psychiatric disorders. Subsyndromal depressive syndromes, for example, are likely in about 25% of individuals with ESRD, and major depression in 5%–22% of this population.[8,9] Delirium and dementia are common, and disorders associated with significant psychiatric morbidity, such as substance abuse and AIDS, can themselves result in the development of renal failure. In a study of data for 175,000 Medicare patients with ESRD, Kimmel and associates[10] found that 9% of the patients were hospitalized for a psychiatric illness during a 1-year period.

Although this article will focus on the use of psychotropic medications, it is important to acknowledge that these medications help only in certain situations. They do not substitute for the skilled provision of psychotherapy and counseling. They cannot replace clarification of complex individual and family matters. It is fortunate that all dialysis programs in the United States are legally mandated to provide access to renal social workers. Ideally, a close working relationship ought to be established to facilitate

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referrals between dialysis staff, consultation psychiatrists, and community mental health practitioners.

Unfortunately, remarkably few data are available on the metabolism and efficacy of psychotropic agents in patients with renal impairment. Most studies are based on a handful of subjects, and well-controlled psychopharmacological trials are rare. Few in vivo studies of the pharmacokinetics of psychotropic agents in normal or ESRD patients are available. More outcomes research is imperative if psychiatric consultants and nephrologists are to manage this substantial patient population.

Clinical, rather than empirical, experience suggests that the majority of psychotropic medications can be safely used with the ESRD population. Most of these drugs are fat soluble, easily pass the blood-brain barrier, are not dialyzable, are primarily metabolized by the liver, and are excreted in bile.[11] Some important considerations and exceptions are noted in the following sections.

PHARMACOKINETICS

Pharmacokinetics is defined as the progress and time course of medications as they work their way through the body.[8] Not only is a major excretory function altered in renal failure and its treatment by dialysis, but other factors are also changed and significantly affect dosing. The factors that are encompassed by the term pharmacokinetics include bioavailability, drug distribution, protein binding, metabolism, and excretion.

Bioavailability refers to the amount of medication that is absorbed and enters the body. In ESRD, absorption may be affected by gastric alkalinizing, which is caused by excess urea generated by the internal urea-ammonia cycle,[12] and by changes in gastrin levels. The use of antacids containing aluminum or calcium may also cause nonabsorbable complexes and chelation, which further diminishes absorption.[13]

The volume of distribution involves the effects of dilution or concentration of medications in the body. A cachectic person has less fluid and less body mass and a decreased volume of distribution. Consequently, a given dose will result in a greater concentration of medication in his/her body than in a noncachectic person.

The issue of protein binding is especially significant in ESRD.[8,10] Most medications are bound in varying degrees to blood albumin. In this state the medication is not available to produce pharmacological effects; it is the free, unbound form that causes efficacy and/or toxicity. Patients with renal failure often have a decreased amount of albumin. Of greater clinical significance is the retention of urea and other substances that compete for plasma protein binding sites; this process typically results in a higher free fraction of plasma protein-bound drug. This effect is particularly important with drugs that both have a high level of plasma protein binding (≥90% in individuals with normal renal function) and are easily displaced from binding sites by urea (e.g., phenytoin and valproic acid [Table 1]). All other factors remaining constant, the greater the protein binding of a medication, the lower the dose required in renal failure.

The degradation, i.e., metabolism, of a medication is probably the area of pharmacokinetics that is least known, particularly since the intermediate products of metabolism are difficult to isolate and identify.[8,10] In renal failure there is a general slowing of chemical reduction and of hydrolysis, but there are normal rates of glucuronidation, microsomal oxidation, and sulfate conjugation. Drug metabolites that are pharmacologically active may be retained in patients with renal insufficiency and may cause adverse effects.

Last, an obvious impact of ESRD is that a major avenue of excretion—through the urine—is absent. The substitution of a machine as the means of this function results in intermittent excretion rather than the continual process that occurs in the individual with normal kidney function. Fortunately, most psychotropic medications are metabolized by the liver and eliminated in bile, which is then excreted in feces. Occasionally, drugs are metabolized to pharmacologically active compounds that are excreted in urine and must be accounted for in ESRD (Table 1).

To summarize, when psychotropic medications are not tolerated by individual patients, it is usually due to altered pharmacokinetics. Such alterations may be directly related to the demographic characteristics and common problems of patients with ESRD, who are likely to be elderly and to have multiple and severe comorbid disorders, protein deficiency, and marked fluid and electrolyte shifts. These features can individually or in combination influence pharmacokinetics. For example, excess gastric alkalinization is not uncommon among ESRD patients, and this condition can affect drug absorption. Similarly, ascites and edema may influence drug distribution by increasing the apparent volume of distribution, and patients with these conditions may therefore require higher initial doses of medication. On the other hand, the dehydration and muscle wasting that is commonly seen in these patients decrease the volume of distribution, and such patients may require lower dosages of the drugs. Last, the high protein-binding affinity of psy-

TABLE 1. Characteristics of Drugs Used in Treating Psychiatric Comorbidity in Patients With Renal Disease[a]

Drug	Active Metabolites	Observed Adverse Reactions	Typical Adult Dose	% Protein Bound in Normal Renal Function	Serum Half-Life in Normal Renal Function (hours unless noted)	Adult Dose in End-Stage Renal Disease	Serum Half-Life in End-Stage Renal Disease (hours unless noted)	Effect of Dialysis	Comments	References
Antidepressants										
Selective serotonin reuptake inhibitors										
Citalopram	Desmethyl-citalopram, didesmethyl-citalopram, citalopram-*N*-oxide	Anxiety, agitation	20–60 q 24 hours	~80%	33–37	10–60 mg/day	43–49	Not removed by hemodialysis	Minimal effect of end-stage renal disease (ESRD) on citalopram kinetics	14–18
Fluoxetine	Norfluoxetine	Anxiety, agitation	20 mg/day	95%	1–4 days (norfluoxetine: 7–15 days)	20 mg/day	1.8 days	Not removed by hemodialysis	No significant differences in fluoxetine and norfluoxetine serum levels in renal failure	15, 16, 19–24
Fluvoxamine	No active metabolites	Anxiety, agitation	100–300 mg/day	~80%	15–22	100–300 mg/day	Similar to values for normal renal function	Not removed by hemodialysis	No significant differences in fluvoxamine serum level in renal failure; manufacturer recommends lower initial doses.	15, 16, 23–25
Paroxetine	No active metabolites	Anxiety, agitation	20–60 mg/day	~95%	17–25	10–30 mg/day	11–55	—	Increased area under the curve (AUC) for paroxetine in ESRD possibly related to metabolite that is an inhibitor of CYP 2D6; reduction in dose recommended.	15, 16, 22–26
Sertraline	No active metabolites	Anxiety, agitation	50–200 mg/day	~98%	24	50–200 mg/day	42–96	Minimal removal by hemodialysis	Minimal changes in kinetics in ESRD; reduction in serum levels in hemodialysis, hypertension	15, 16, 22, 23, 27–29

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Tricyclics										
Amitriptyline	Nortriptyline, hydroxy-amitriptyline, hydroxy-nortriptyline	Sleep disturbance, forgetfulness, confusion, delirium, hallucinations, paranoia	25 mg q 8 hours	—	32–40	25 mg q 8 hours	32–40	Not removed by hemodialysis	Elevated conjugated metabolites observed in renal failure; probably no difference in dosing; use of therapeutic drug monitoring (TDM) with serum level of 75–175 μg/liter may guide therapy if drug is used for depression.	11, 15, 22, 24, 30, 31
Clomipramine	Desmethyl-clomipramine		100–250 mg q 24 hours	97%	19–37 (desmethyl-clomipramine: 54–77)	—	—	—	Few data on use in ESRD	24, 32
Desipramine	2-hydroxy-desipramine	Sleep disturbance, forgetfulness, confusion, delirium, hallucinations, paranoia	100–200 mg q 24 hours	—	12–54	75–125 mg/day	—	Not removed by hemodialysis or by continuous ambulatory peritoneal dialysis (CAPD)	Effective in small trial for depression in renal disease; use of TDM with serum level of 100–160 μg/liter may guide therapy if drug is used for depression; unconjugated amine and hydroxylated-metabolites not removed by dialysis	11, 15, 22, 24, 33–35
Doxepin	Desmethyl-doxepin		25 mg q 8 hours	80%–85%	8–25	25 mg q 8 hours	10–30	Not removed by hemodialysis or by CAPD		11, 24, 36
Imipramine	Desipramine	Sleep disturbance, forgetfulness, confusion, delirium, hallucinations, paranoia	25 mg q 8 hours	—	6–20	25 mg q 8 hours	—	Not removed by hemodialysis or by CAPD		11, 15, 24

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Nortriptyline	10-Hydroxy-nortriptyline, E-10-hydroxy-nortriptyline, Z-10-hydroxy-nortriptyline		25 mg q 6–8 hours	93%	18–93	25 mg q 6–8 hours	15–66	Not removed by hemodialysis or by CAPD	Use of TDM with serum level of 50–150 µg/liter may guide therapy if drug is used for depression	11, 24, 37
Other antidepressants										
Amoxapine	8-Hydroxy-amoxapine; 7-hydroxy-amoxapine		75–200 mg/day	80%	8–30 (8-hydroxy-amoxapine: 30; 7-hydroxy-amoxapine: 4–6.5)	75–200 mg/day	—	—	Few data on use in ESRD	23, 24, 38
Bupropion	Hydroxy-bupropion, threo-bupropion	Hallucinations, insomnia, agitation	100 mg q 8 hours	~85%	10–21	100 mg/day to 100 mg q 8 hours	—	—	Risk for seizures with elevated serum levels of bupropion or its metabolites in renal disease; use of TDM of bupropion (serum level of 10–50 µg/liter), hydroxy-bupropion (<1200 µg/liter), and threo-bupropion (<400 µg/liter) may guide therapy to avoid toxicity	15, 23, 24, 31
Maprotiline	Desmethyl-maprotiline, maprotiline-*N*-oxide		75–150 mg/day	—	48–51	37.5–100 mg/day	—	—		23, 39, 40
Mirtazapine	Demethyl-mirtazapine		15–45 mg/day	85%	20–40 (demethyl-mirtazapine: 25)	7.5–22.5 mg/day	—	—	Clearance reduced by approximately 50% in renal disease; no clear role for TDM	31, 41, 42
Nefazodone	Multiple, including hydroxy-nefazodone		50–150 mg q 12–24 hours	>99%	3–5 (hydroxy-nefazodone: 2.5)	50–150 mg q 12–24 hours	3.0–5.8; hydroxynefazodone: 4.4	Minimal removal by hemodialysis	Primarily nonrenal elimination of drug; no clear role for TDM; not for first-line therapy due to potential for serious hepatotoxicity	23, 31, 43, 44

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Trazodone	Meta-chloro-phenyl-piperazine	Hypomania	50–400 mg q 24 hours	~90%	4–11	No data	No data	—	For 50 mg/day dose, predialysis serum levels of 85–89 ng/ml and postdialysis serum levels of 29–40 ng/ml; no clear role for TDM	15, 23, 24, 31, 45–47
Venlafaxine	*O*-desmethyl venlafaxine		37.5–225 mg/day (extended release)	~30%	4 (*O*-desmethyl venlafaxine: 4)	37.5–112.5 mg/day (extended release)	6–11 (*O*-desmethyl venlafaxine: 9)	Not removed by hemodialysis	No clear role for TDM	23, 24, 31, 48
Antimanic agents										
Lithium	None		900–1200 mg/day	—	14–28	200–600 mg/day	40	Considerable removal by hemodialysis; variable reports on removal by CAPD	Administration of single dose after dialysis recommended	11, 23, 24, 29, 49
Valproic acid/ divalproex	Unclear whether metabolites are active		15–60 mg/kg per day	80%–90% (dose dependent)	6–17	15–60 mg/kg per day	—	Modest removal by hemodialysis	Possible increased risk of pancreatitis in ESRD; increased free serum levels in ESRD; use free valproic acid serum levels with TDM	23, 49, 50, 51, 52
Antipsychotics										
Typical										
Chlorpromazine (CPZ)	CPZ-*N*-oxide, CPZ sulfoxide, 7-hydroxy-CPZ, nor1-CPZ, nor2-CPZ, nor2-CPZ sulfoxide, 3-hydroxy-CPZ		50–400 mg/day	—	11–42	—	11–42	—		11, 53, 54

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Haloperidol	Hydroxy-haloperidol (unclear whether other metabolites are active)		1–2 mg q 8–12 hours	90%	14–26	1–2 mg q 8–12 hours	Similar to values for normal renal function	—	<1% of drug excreted in urine	24, 55–57
Perphenazine	Activity of metabolites unknown		4–16 mg b.i.d.– q.i.d.	—	9.5	—	—	—		58, 59
Thioridazine	Mesoridazine (twice the potency of thioridazine), sulforidazine	Prolonged QTc interval	50–800 mg/day	—	21–24	—	—	—	Contraindicated in patients with prolonged QTc interval or concurrent fluoxetine, paroxetine, or fluvoxamine therapy; best avoided in renal disease because of prolonged QTc interval and because risk for life-threatening arrhythmias may be higher with electrolyte shifts	60
Atypical										
Aripiprazole	Dehydro-aripiprazole		10–30 mg/day	>99%	75–146	10–30 mg/day	Compared with values for normal renal function, C_{max} is 36% higher for aripiprazole and 53% higher for dehydro-aripiprazole; AUC is 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole	—	Significant drug interactions with other drugs metabolized by 2D6 or 3A4; renal elimination of <1% of dose; no adjustment in dose in renal insufficiency	61

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Clozapine	*N*-desmethyl-clozapine	Delirium with psychosis on withdrawal	12.5–450 mg, slowly titrated	97%	8–12 (*N*-desmethyl-clozapine: 13.2)	Titrate to response and utilize TDM	—	—	Titrate dose to response; TDM may assist dosing in unclear circumstances; avoid serum levels > 400 µg/liter	62–65
Olanzapine	*N*-desmethyl olanzapine, olanzapine 10-*N*-glucuronide		5–20 mg	93%	32–38	5–20 mg	32–38	—	Dose adjustment not necessary in renal failure, per manufacturer	66, 67
Quetiapine	7 hydroxy-quetiapine, *N*-dealkylated quetiapine		150–750 mg/day divided b.i.d. or t.i.d.	83%	6	150–750/ day divided b.i.d. or t.i.d.	—	—	Dose adjustment not necessary in renal failure, per manufacturer	68
Risperidone	9-Hydroxy-risperidone		1–3 mg b.i.d.	~90%	3–30 (9-hydroxy-risperidone: 19)	0.5–1.5 mg b.i.d.	9–Hydroxy-risperidone: 25	—	Wide variation in clearance noted between poor and extensive metabolizers; clearance of sum of risperidone and 9-hydroxy-risperidone reduced by 60% in renal failure	69, 70
Ziprasidone	Inactive metabolites		20–80 mg b.i.d.	99%	7	10–80 mg b.i.d.	—	—	No adjustment required for creatinine clearances of 10–60 ml/min, per manufacturer; electrolyte fluctuations in dialysis may increase cardiac risk	71, 72

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Anxiolytics/ hypnotics										
Alprazolam	α-Hydroxy-alprazolam (<15% of alprazolam)	Hallucin-ations	0.25–5 mg t.i.d.	80%	9–19	0.25–5 mg t.i.d.	9–19	Minimal removal by hemodialysis	Increased free fraction of plasma protein-bound drug in ESRD; minimal differences in dialysis-dependent patients	11, 23, 24, 73–76
Buspirone	1-pyrimidinyl-piperazine		5 mg q 8 hours	86%	0.5–2.5 (1-pyrimidinyl-piperazine: 6.3)	5 mg q 8 hours	1–5 (1-pyrimidinyl-piperazine: 9)	Not removed by hemodialysis	Considerable interindividual and intraindividual variability in kinetics in ESRD; patients with renal failure may benefit from a 25%–50% dose reduction	11, 77–80
Chlordiazepoxide	Multiple		15–100 mg/ day	90–98%	5–30	7.5–50 mg/ day	—	—	Decreased protein binding, increased clearance in renal disease	11, 23, 55
Clorazepate	Desmethyl-diazepam		15–60 mg/ day p.o.	Desmethyl-diazepam: 97%	Desmethyl-diazepam: 57.3	15–60 mg/ day p.o.	Desmethyl-diazepam: 36.1	—	Increased free fraction desmethyl-diazepam resulting in similar free serum levels in normal renal function and in renal insufficiency	23, 81
Clonazepam	No active metabolites		0.5 mg t.i.d.	85%	18–80	0.5 mg t.i.d.	—	Not removed by hemodialysis		23, 82, 83
Diazepam	Desmethyl-diazepam; oxazepam	Delusions, hallucin-ations	5–40 mg/ day	98%	92 (desmethyl-diazepam: 57.3)	5–40 mg/ day	37 (desmethyl-diazepam: 36.1)	Not removed by hemodialysis	Elevated free serum levels of diazepam in ESRD; increased free fraction of desmethyl-diazepam resulting in similar free serum levels in normal renal function and renal insufficiency	23, 24, 55, 81, 84–86

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Lorazepam	No active metabolites		1–2 mg b.i.d. or t.i.d.	85%	9–16	0.5–2 mg b.i.d.	32–70	Not removed by hemodialysis	Manufacturer does not recommend use in ESRD	11, 23, 24, 55, 87
Midazolam	α-Hydroxy-midazolam conjugate	Prolonged sedation	1.25 mg i.v., titrated to response	95%	1–12	1.25 mg i.v., titrated to response	1–12 (α-Hydroxy-midazolam conjugate: 50.4–76.8)	—	Possible increased effect due to reduced protein binding	23, 24, 55, 88
Oxazepam	No active metabolites		30–120 mg/day	variable; 86–99%	6–25	30–120 mg/day	25–90	Not removed by hemodialysis		11, 23, 24
Temazepam	No active metabolites		15–30 mg h.s.	96%	4–10	15–30 mg h.s.	—	Not removed by hemodialysis or by continuous ambulatory peritoneal dialysis		11, 23, 24
Triazolam	α-Hydroxy-triazolam	Hallucinations, paranoia	0.125–0.5 mg/day	89%	2–4	0.125–0.5 mg/day	2.3	Not removed by hemodialysis or by CAPD		23, 24, 89
Zaleplon	No active metabolites		5–20 mg h.s.	~60%	1	Possible adjustment in dose range to 5–10 mg h.s.	—	—	No dose adjustment necessary for mild to moderate renal impairment, per manufacturer; drug not studied in ESRD	90
Zolpidem	No active metabolites		10 mg/day	92%	2–3	Reduce dose by 50%	4–6		Increased free fraction in renal disease	20, 91

[a]Adapted from *Therapy in Nephrology and Hypertension: A Companion to Brenner and Rector's The Kidney, 2nd ed.,* edited by Hugh R. Brady and Christopher S. Wilcox, 2003, by permission of the publisher WB Saunders.

chotropic medications in renal failure may leave a larger proportion of a given dose of medicine unbound and consequently more available for efficacy, toxicity, or elimination.

Given these multiple and interacting factors, it is not surprising that dosing often involves trial and error. The Physicians' Desk Reference generally recommends that patients with ESRD be administered no more than two-thirds the ordinary or maximum dose of most psychoactive drugs.[92] However, in our clinical experience and in our examination of the literature, we have observed that the majority of patients with ESRD both tolerate and require ordinary doses of most psychotropic medications. Toxicity is usually obvious, and we would caution more against undermedicating patients than against overmedication.

TRADITIONAL AND ATYPICAL NEUROLEPTIC MEDICATIONS

Pharmacological treatment of schizophrenia has been revolutionized by the use of the atypical neuroleptics, including clozapine, risperidone, and olanzapine. Unlike traditional neuroleptics, this new generation of major tranquilizers effectively treats the negative symptoms of the disease, such as emotional blunting and apathy. However, little is known about their properties in patients with ESRD, and considerable wariness is necessary. Olanzapine, for example, is largely metabolized by the liver, but its metabolites are excreted in urine.[66] Single-dose studies in renal impairment indicate that special dosing is not required, but multiple dose studies have not been conducted. Olanzapine may also aggravate diabetes mellitus,[93] a common comorbidity for many ESRD patients. Ziprasidone is probably best avoided in ESRD patients, since the risk of life-threatening arrhythmias related to prolongation of QT intervals is higher with electrolyte shifts. The clearance of risperidone and its active metabolite is reduced by 60% in patients with renal disease.[69]

It is not uncommon for patients with renal disease to have comorbid delirium, and many of these cases are etiologically complex and require rapid treatment of symptoms such as agitation. Dementia is also becoming more prevalent in this aging population. Pharmacological symptom management of agitation usually entails administration of the traditional neuroleptics, such as haloperidol.[94] In acutely hospitalized and delirious patients, haloperidol is commonly administered parenterally—often through a slow, intravenous push.[95] Less than 1% of haloperidol is excreted in the urine, and it appears to be a safe medication in ESRD. This method is not formally approved, however, and there have been rare cases of torsade-de-pointes-type arrhythmias. Although we have not observed and are not aware of haloperidol-induced arrhythmias in patients with renal disease, the electrolyte shifts commonly observed in these patients may theoretically render them at higher risk for this adverse event. Thioridazine and mesoridazine are best avoided, given concerns about abnormality in cardiac conduction observed in ESRD patients. Again, while the newer atypical neuroleptic agents hold promise for the future treatment of delirium,[96] their effects in delirious, schizophrenic, or demented patients with renal impairment have not been systematically investigated.

ANTIANXIETY AND SEDATING MEDICATIONS

Anxiety is one of the most common psychological symptoms seen in this population, and it may be particularly severe during or immediately preceding dialysis treatments.[1] Rapid removal of fluid and electrolytes can produce nausea, vomiting, hypotension, and muscular cramps and can also result in considerable anxiety. Generalized anxiety about the future, apprehension about one's ability to adjust to the ongoing demands of treatment and expectations of loved ones, as well as concerns about sexual performance, can all contribute to anxiety. Pharmacological management is either directed at acute episodes of panic and anxiety or at more generalized nervousness. Benzodiazepines are metabolized in the liver, and dose reduction is generally not necessary in ESRD (although for use of midazolam and chlordiazepoxide, cautious dosing may be required due to changes in plasma protein binding associated with those drugs).[55,88] It is not unusual to give ordinary doses of diazepam, alprazolam, and clonazepam before or during dialysis treatments. Lorazepam is also often given at ordinary doses, although the half-life of lorazepam may be prolonged in ESRD.[55] Considerable variation in pharmacokinetics is observed with buspirone in individuals with ESRD; there is an increase in the half-life of both the parent compound and its active metabolite.[77–79] Since the dizziness associated with buspirone could accentuate the postural hypotension that is often observed in ESRD patients, doses of this medication should be carefully titrated. Selective serotonin reuptake inhibitors (SSRIs), which will be discussed in the section on antidepressants, are being increasingly used to treat panic and generalized anxiety disorders.

Insomnia is also quite prevalent in patients with chronic kidney disease and may occur secondary to sleep

apnea, restless leg syndrome, cramps, and discomfort associated with peripheral neuropathy. Identification and treatment of these individual conditions will correct many instances of insomnia. Nonpharmacological treatments, e.g., behavioral management and instruction in sleep hygiene practices, should be tried. If these treatments are ineffective, a hypnotic such as temazepam or zolpidem can be used on a short-term basis. Although not officially recommended, time-limited use often becomes regular maintenance treatment for many patients.

Zaleplon is a new nonbenzodiazepine hypnotic agent indicated for short-term treatment of insomnia. The manufacturer maintains that since less than 1% of the drug is excreted by the kidneys, the pharmacokinetics are not altered in patients with renal insufficiency. However, plasma concentrations of zaleplon metabolites are substantially increased in patients with renal impairment, and the medication has not been adequately studied in hemodialysis populations.

ANTIDEPRESSANT MEDICATIONS

Reviews of antidepressant management of ESRD have consistently found both SSRI and tricyclic antidepressants to be beneficial.[97] Although the greater body of experience is with the tricyclics, these medications have largely been supplanted by the newer generation of antidepressants. Tricyclics ought to be reserved for treatment-resistant depression (or other indications, such as peripheral neuropathy). In ESRD, the hydroxylated metabolites of tricyclics contribute to both the therapeutic and the toxic effects of these drugs. Amitriptyline and imipramine continue to be widely used for analgesia of neuropathic pain, while trazodone is commonly used for insomnia.

SSRIs are remarkably beneficial in ESRD, but their effects have not been sufficiently researched.[1,8] Fluoxetine is the best studied medication in this class, and it appears to be both nontoxic and efficacious in patients with ESRD.[19] Even in anephric patients, the kinetic profile of single doses of fluoxetine is unchanged. A study of multiple doses concluded that renal function does not significantly alter serum levels of either fluoxetine or norfluoxetine.[20,21]

Sertraline has not been studied as intensively in this population, but it is also widely prescribed. Like fluoxetine, it is metabolized in the liver, and excretion of the unchanged drug in urine is an insignificant route of elimination. Pharmacokinetic studies of people with mild-to-severe renal impairment and matched comparison subjects have shown no significant differences between groups.[22,27] Sertraline has been used to help prevent sudden hemodialysis-related hypotension.[28]

Citalopram kinetics are similar to those of sertraline and fluoxetine, in that they are minimally changed in patients with ESRD, and dose adjustment is probably not necessary.[14,98] By way of contrast, plasma concentrations of paroxetine hydrochloride are increased in people with renal impairment, and the recommended initial dose for patients with severe renal insufficiency (10 mg) is half that for adults with normal kidney function.[26,99]

Several non-SSRI antidepressant medications should be avoided or used with caution in ESRD. For example, little is known about the pharmacokinetics of nefazodone hydrochloride in patients with chronically impaired renal function.[43,44] Careful dose adjustment is also necessary with venlafaxine, which, along with its metabolites, is chiefly eliminated in urine. Venlafaxine's elimination half-life is prolonged and its clearance is reduced in chronic renal insufficiency or ESRD.[48] Regular monitoring of blood pressure is recommended for patients who receive this drug. Bupropion hydrochloride has active metabolites that are almost completely excreted through the kidney. The metabolites may accumulate in dialysis patients and predispose these patients to seizures.

Theoretically, care must be taken with patients receiving concurrent low therapeutic index drugs metabolized by cytochrome P450 enzyme systems. A few such drugs used in this population include agents metabolized by cytochrome P450 3A4 (e.g., tacrolimus, sildenafil, cyclosporine), while a number of antidepressants (e.g., nefazodone, fluvoxamine, paroxetine [a weak inhibitor], fluoxetine/norfluoxetine, sertraline, and valproic acid [also a weak inhibitor]) are inhibitors of this isoenzyme.[1]

MOOD STABILIZERS

For many years, lithium has been the primary pharmacologic treatment for bipolar affective disorder. In general psychiatric practice it is being replaced by classic anticonvulsant medications, such as divalproex and carbamazepine. For the minority of bipolar disorder patients with ESRD who require lithium (and do not respond to the anticonvulsants), treatment involves administration of a single dose (usually 600 mg) after each dialysis session. Because it is a small molecule that is readily dialyzed, lithium is entirely eliminated by dialysis, and a single postdialysis dose will result in a steady serum level.[100] Ideally, in order to establish the proper dose, serum lithium levels should

be obtained immediately before dialysis. Because of a postdialysis redistribution effect, the serum lithium level obtained immediately after dialysis will often be lower than that observed later. Lithium is also used to augment the therapeutic effects of antidepressants in patients with treatment-resistant unipolar depression, and a smaller dose of lithium, e.g., 300 mg, may be given to such patients after a dialysis session.

There has been controversy in the past as to whether lithium is nephrotoxic. New evidence suggests that it indeed can lead to renal insufficiency and even ESRD; however, a recent long-term follow-up study has found that when the drug is discontinued, renal function will often improve.[101] If renal impairment is detected in a bipolar disorder patient who is receiving lithium, efforts should be made to substitute other mood stabilizing drugs, although such substitution is not always possible for some sensitive bipolar disorder patients.

Seizures are not uncommon in the renal disease population, and nephrologists are accustomed to prescribing anticonvulsant medications. Valproic acid is likely to be helpful as a mood stabilizer, but psychiatrists should be aware that free serum levels may become elevated in patients with renal disease, and individual cases of pancreatitis have been reported.[50,51]

CONCLUSIONS

In summary, most psychotropic medications are well tolerated and efficacious in the treatment of patients with ESRD and renal insufficiency. There are exceptions for which tolerance and safety are questionable, and we have attempted to identify many of those drugs in this review. Clinical experience is not an adequate substitute for systematic and well-designed empirical research. Particularly for the newer medications, there has been a dearth of investigations, and we hope that this article stimulates additional psychopharmacological research.

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