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FROM THE ANALYST'S COUCH

Schizophrenia therapy: beyond atypical antipsychotics

Eric M. Snyder and Melanie R. Murphy



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Antipsychotics remain the current standard of care for mental disorders including schizophrenia (~1% prevalence) and bipolar mania (~3% prevalence), and generate over US$16 billion worldwide in annual sales (FIG. 1; TABLE 1). However, a large trial known as CATIE, sponsored by the US National Institutes of Health, found that 74% of patients discontinue use within 18 months of therapy due to either poor tolerability or incomplete efficacy[1], indicating a need for novel therapies.

The first generation of antipsychotics — termed conventional or 'typical' antipsychotics — such as haloperidol, inhibit dopamine D_2 receptors and are moderately effective in treating positive symptoms of schizophrenia (for example, hallucinations), but may cause extrapyramidal movement disorders. Second-generation 'atypical' antipsychotics — such as Lilly's Zyprexa (olanzapine), Johnson & Johnson's Risperdal (risperidone) and AstraZeneca's Seroquel (quetiapine) — inhibit D_2 receptors in conjunction with other receptors (notably 5-hydroxytryptamine 2A (5-HT_{2A}) receptors) (TABLE 1). Atypical antipsychotics have proved less likely to cause movement disorders, but are associated with weight gain, prolactin and glucose elevation, and sedation.

Zyprexa is widely regarded as being the most effective atypical antipsychotic on the market, but in the past 3 years, issues related to side effects have led to the drug losing nearly half its market share, as well as over 28,000 lawsuits, again indicating the need for drugs with better side-effect profiles. Furthermore, with all of the currently marketed atypicals facing generic competition within 5 years, there is a considerable market opportunity for new branded antipsychotics.

A new approach: mGluRs

In September 2007, Eli Lilly announced results of a 4-week Phase II trial of their metabotropic glutamate receptor 2/3 (mGluR2/3) agonist LY2140023 for schizophrenia. Although LY2140023 exhibited slightly less efficacy than Zyprexa in reducing positive symptoms, it nonetheless delivered significant improvement[2]. Importantly, while treatment with Zyprexa was associated with weight gain, patients who received LY2140023 actually lost an average of 0.5 kg. These data indicate that mGluR agonists could represent a breakthrough in the search for a better-tolerated antipsychotic.

Indeed, this mechanism appears so promising that Eli Lilly, Merck, Johnson & Johnson and Pfizer (as well as partners Addex and Taisho) are all racing to develop mGluR-targeted drugs for schizophrenia. For example, early this year, Merck expanded their commitment to develop a new antipsychotic by entering into an exclusive worldwide license agreement with Addex for their preclinical, positive allosteric mGluR5 modulator ADX63365. This is Merck's second deal for an mGluR modulator for schizophrenia, having previously partnered with Taisho for another preclinical compound.

Eli Lilly clearly holds the lead in the mGluR race, with proof-of-concept data in hand and Phase III trials anticipated to begin later this year, whereas other competitors are not yet in the clinic. However, it remains to be seen whether Eli Lilly's LY2140023 will prove superior in the long run. This compound is a traditional, orthosteric agonist that provides continual activity as long as it is bound to the receptor. Conversely, allosteric modulators such as those being developed by Addex provide activity only when the endogenous agonist is present. This might provide a more normal pattern of signalling and be more attractive for long-term use.

The precise mechanism by which LY2140023 and other mGluR-targeted agents have efficacy in schizophrenia is not understood, although there may be some overlap with previously established mechanisms. Glutamate and dopamine axons converge on the medium spiny neurons of the striatum[3,4] (FIG. 2). In addition, mGluR2/3 agonists have been shown to inhibit dopamine release, demonstrating functional interconnectivity of these two neurotransmitter pathways. It remains possible that mGluR2/3 agonists may in fact target the conventional pathway of dopamine D_2 antagonism. Alternatively, mGluR2/3 may form a complex with 5-HT_{2A} receptors, suggesting that mGluR activation can regulate 5-HT signalling[5].

Addex and Merck's ADX63365 targets mGluR5, which has no known effect on dopamine signalling, but which can modulate the signalling of the ionotropic NMDA (*N*-methyl-D-aspartate) glutamate receptor, another receptor that has long been thought to be associated with schizophrenia. This pathway may have additional benefits: while Merck and Addex still await human clinical data for ADX63365, animal studies suggest that this compound can improve cognition as well as positive symptoms. Thus, in addition to being safer than atypicals, mGluR agonists might offer improved efficacy in the cognitive domains of schizophrenia.

Outstanding issues

Long-term studies of mGluR-targeted agents have yet to be conducted and it remains to be seen whether the efficacy seen in Eli Lilly's 4-week study can be maintained. Furthermore, although mGluRs appear to offer good tolerability, longer-term trials are needed to gauge safety. If mGluR-targeted drugs can mimic the profile seen so far with Eli Lilly's LY2140023, it will be interesting to see how physicians would use mGluR agonists. Would they be prescribed independently, even though they may not have the efficacy of their atypical predecessors? Would they be used as adjunctive therapies, in combination with lower doses of atypicals? This cocktail therapy model is being pursued by Acadia with their 5-HT_2 inverse agonist primavanserin, which improves the efficacy of low doses of risperidone without causing weight gain. A third possibility is that mGluR-targeted agents could be used in conjunction with primavanserin, creating a selective, targeted therapy with few side effects.

Overall, the development of mGluR-targeted drugs for schizophrenia represents an opportunity for a new class of drugs that might represent a superior treatment option to that of currently available antipsychotics, as well as an advance in the understanding of the molecular basis for therapies for psychiatric disorders. ▸

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BEYOND ATYPICALS | **MARKET INDICATORS**

The market for drugs for schizophrenia has grown tenfold in the past decade (FIG. 1, TABLE 1). In 2007, Risperdal and Zyprexa led the worldwide market with $4.7 billion in sales each. Zyprexa sales have grown, despite continuing concerns with side effects. In addition to the need for novel antipsychotics with improved safety and efficacy profiles, the approaching patent expirations of leading products is creating a challenge for the pharmaceutical industry. Recent data indicate that agents that target mGluRs could represent a promising new class of antipsychotics, and such agents are now being developed by several companies (TABLE 2).

Eric M. Snyder and Melanie R. Murphy are at Mehta Partners Global BioPharmaceutical Investments, 276 Fifth Avenue Suite 1100, New York 10001, USA.
e-mail: snyder@mpglobal.com

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Competing interests statement
The authors declare competing financial interests: see web version for details.

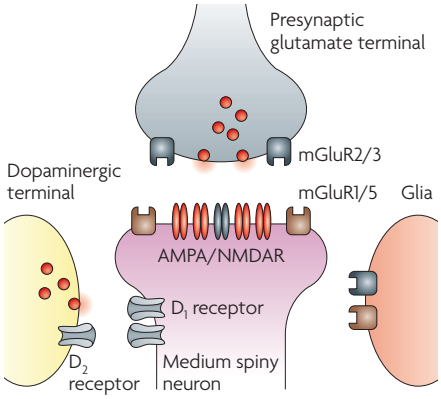


Figure 2 | **Metabotropic glutamate receptors (mGluRs) in the synapse.** The mechanisms by which mGluR agonists can alleviate schizophrenia remains unclear. Group 1 mGluRs (mGluR1 and 5) are located post-synaptically, peripheral to the post-synaptic density where they may regulate both glutamatergic and dopaminergic signalling. Group 2 mGluRs (mGluR2 and 3) are found pre-synaptically, directly modulating glutamate release. In addition, these receptors can be found in glia.

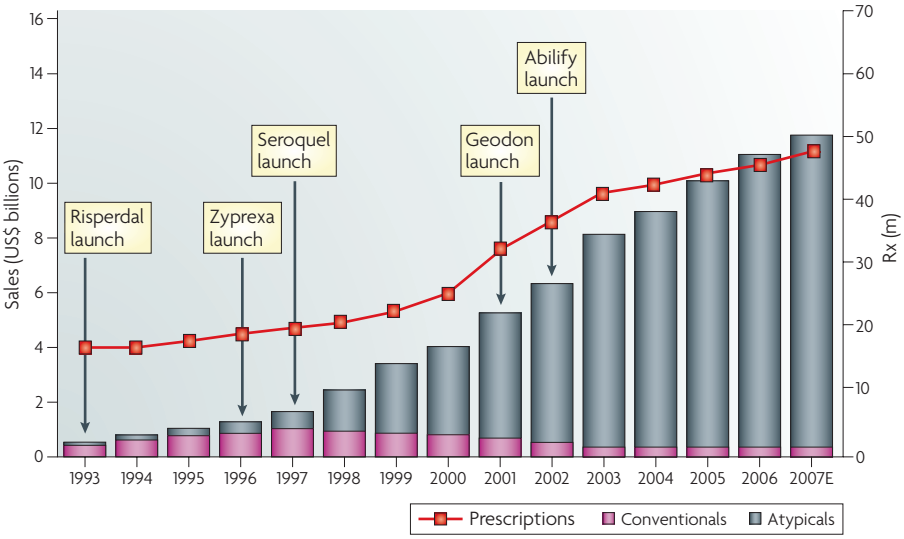


Figure 1 | **Worldwide sales of drugs for schizophrenia, 1993–2007.** The schizophrenia drug market has grown from less than $1 billion annually in 1993 to more than $10 billion. This rapid growth has followed the introduction of Risperdal in 1993, followed by Zyprexa, Seroquel, Geodon (ziprasidone; Pfizer) and Abilify (aripiprazole; Bristol–Myers Squibb). Annual prescriptions have increased from ~20 million to more than 40 million in this time. Source: IMS.

Table 1 | **Currently marketed antipsychotics**

Company	Launched drug	Mechanism of action	2006 sales worldwide (US$)	Patent expiration
Johnson & Johnson	Risperdal (risperidone)	D_2, 5-HT, α-$_{2A}$ antagonist	4.1 billion	2008
Eli Lilly	Zyprexa (olanzapine)	D_2, 5-HT_2, M_{1-4}, H_1 antagonist	4.3 billion	2011
Pfizer	Geodon (ziprasidone)	D_2, 5-HT_2 antagonist	0.8 billion	2012
AstraZeneca	Seroquel (quetiapine fumarate)	D_2, 5-HT_2, 5-HT_6, H_1 antagonist	3.6 billion	2012
Bristol–Myers Squibb	Abilify (aripiprazole)	D_2 partial agonist	1.2 billion	2014

5-HT, 5-hydroxytryptamine receptor; α-2_A, α-2_A adrenoceptor; D_2, dopamine receptor 2; H_1, histamine receptor 1; M_{1-4}, muscarinic receptors 1–4.

Table 2 | **Next-generation antipsychotics**

Company	Pipeline drug	Mechanism of action	Phase	POC
Eli Lilly	LY2140023	mGluR2/3 agonist	II/III	Yes
Acadia	Primavanserin	5-HT inverse agonist	II/III	Yes
Merck/Addex	ADX63365	mGluR5 PAM	Preclinical	No
Johnson & Johnson/Addex	NA	mGluR2/3 PAM	Preclinical	No
Merck/Taisho	NA	mGluR agonist	Preclinical	No
Pfizer/Taisho	TS-032	mGluR agonist	Preclinical	No

5-HT, 5-hydroxytryptamine; mGluR, metabotropic glutamate receptor; NA, not applicable; PAM, positive allosteric modulator; POC, proof-of-concept.

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