Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Editor's choice

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
19 July 2012
Number of times this article has been viewed

Roger M Pinder

Editor-In-Chief, Neuropsychiatric Disease and Treatment

Schizophrenia remains one of the most debilitating and intractable illnesses in psychiatry. Despite the availability of effective drug treatment since the beginning of the psychopharmacological era in the early 1960s with the introduction of the first antipsychotic chlorpromazine, the subsequent development of second generation or atypical antipsychotics, and the effectiveness of certain types of psychotherapy, many patients are unresponsive and remain unwell for several years or relapse after apparent response. Only clozapine has proven efficacy in treatment-resistant schizophrenia, but many patients still do not respond. Polypharmacy is common, with many physicians choosing to augment rather than switch medications. Schizophrenia may be in part a neurodevelopmental disorder and involve changes in brain structure, and credence has been given to the idea that the prodromal phase, before overt symptoms have appeared, should already have been addressed with aggressive treatment. Various aspects of schizophrenia and its treatment, as well as the associated use of antipsychotic drugs in the treatment of the manic phase of bipolar disorder and Tourette syndrome, have been covered in the pages of *Neuropsychiatric Disease and Treatment* during the first half of 2012.

The latest "kids on the block" to be approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia are asenapine,[1] a tetracyclic with structural similarities to the antidepressant mirtazapine and possessing a broad clozapine-like pharmacological profile, and lurasidone,[2] a benzoisothiazole derivative related to ziprasidone that shares with many atypical antipsychotics a profile of antagonism at dopamine D_2 and serotonin 5-HT_{2A} receptors as well as partial agonism at 5-HT_1 receptors. Asenapine is also approved worldwide for the treatment of acute mania in bipolar disorder, while lurasidone is still under clinical investigation. Neither drug seems to offer any major advantage in terms of efficacy in schizophrenia, although side-effect profiles do differ between the various atypical antipsychotics. Asenapine should be evaluated in treatment-resistant schizophrenia and in patients with predominantly negative symptoms because of its pharmacological similarity to clozapine.

Whether to add another medication to the therapeutic regimen of a patient who is only partially responding or to substitute a different medication is a topical dilemma in psychiatry, particularly with regard to schizophrenia. In a post-hoc analysis of a large group of schizophrenic patients participating in a 12-month international observational study,[3] it was clear that the worsening condition of a patient or the lack of any meaningful improvement prompted physicians to switch to another antipsychotic

Correspondence: Roger M Pinder
2, St Wilfrids Court, Monkgate,
York YO31 7UQ, UK
Tel +44 1904 646684
Email roger.pinder@gmail.com

medication. On the other hand, patients showing some degree of improvement were more likely to receive augmentation with another antipsychotic to boost response. Patients partially stabilized on other first or second generation antipsychotics and with persistent negative symptoms were more likely to do well on either olanzapine or asenapine during the course of two 26-week randomized trials in 949 subjects.[1] In Japan, a large healthcare database analysis suggested that, where monotherapy was used in schizophrenic outpatients, olanzapine was more likely to be used, and for a longer duration, than risperidone.[4]

Few of the atypical antipsychotics have been evaluated in treatment-resistant schizophrenia, and clozapine remains the gold standard and the only FDA-approved medication for the indication. A review of the role of aripiprazole, which differs in pharmacology from the other atypical antipsychotics in being a partial dopamine agonist, concluded that adding aripiprazole to clozapine in patients who were resistant or intolerant to the latter was probably beneficial.[5] The role of aripiprazole as monotherapy in treatment-resistant schizophrenia is inadequately studied. Both aripiprazole and other atypical antipsychotics of different pharmacology, when administered for 6 months to first episode schizophrenic patients in Japan, decreased frontal lobe glutaminergic neurotransmission.[6] This is interesting in that the glutamate system is one of the targets for development of novel antipsychotics.

Other uses of antipsychotics were also reviewed. Antipsychotics have long been used in the treatment of Tourette syndrome, while the newer atypical drugs are all effective in the treatment of acute mania in bipolar disorder. Paliperidone extended release (ER), as expected from its close relationship to risperidone, was effective as monotherapy in the treatment of acute mania in bipolar disorder, although its higher cost than generically available olanzapine and risperidone may limit its usefulness in this indication. The role of paliperidone ER as an adjunctive agent or for long-term use needs further investigation.[7] A review of the role of antipsychotics in the treatment of Tourette syndrome[8] concluded that, while the two FDA-approved drugs, haloperidol and pimozide, are used on the basis of old and inadequate trials, there is currently insufficient evidence on second generation antipsychotics for approval with the possible exception of risperidone. Given that the pathophysiology of Tourette syndrome is thought to involve a dysfunction of basal ganglia circuitry and hyperactive dopaminergic innervations, it is logical to expect that antidopaminergic agents like antipsychotics would be effective.

Finally, confirmation of the marked impairment in reinforcement learning in schizophrenia was demonstrated in a study comparing 25 clinically stable patients with a similar group of matched healthy controls.[9] Using a simple gambling paradigm, schizophrenic patients showed impaired reward-based learning that was independent of medication status but correlated with the severity of negative symptoms.

Disclosure

This author reports no conflicts of interest in this work.

References

1. Cazoria P, Mackle M, Zhao J, Ha X, Szegedi A. Safety and tolerability of switching to asenapine from other antipsychotic agents: pooled results from two randomized multicenter trials in stable patients with persistent negative symptoms in schizophrenia. *Neuropsychiatr Dis Treat*. 2012; 8:247–257.
2. Caccia S, Pasina L, Nobili A. Critical appraisal of lurasidone in the management of schizophrenia. *Neuropsychiatr Dis Treat*. 2012;8: 155–168.
3. Ascher-Svanum H, Brnabic AJM, Lawson AH, et al. Comparison of patients undergoing switching versus augmentation of antipsychotic medications during treatment for schizophrenia. *Neuropsychiatr Dis Treat*. 2012;8:113–118.
4. Ye W, Ascher-Svanum H, Tanji Y, Flynn JA, Takahashi M, Conley RR. Antipsychotic monotherapy among outpatients with schizophrenia treated with olanzapine or risperidone in Japan: a healthcare database analysis. *Neuropsychiatr Dis Treat*. 1012;8:259–266.
5. Mossaheb N, Kaufmann RM. Role of aripiprazole in treatment-resistant schizophrenia. *Neuropsychiatr Dis Treat*. 2012;8:235–244.
6. Goto N, Yoshimura R, Kakeda S, et al. Six-month treatment with atypical antipsychotic drugs decreased frontal-lobe levels of glutamate plus glutamine in early-stage first-episode schizophrenia. *Neuropsychiatr Dis Treat*. 2012;8:119–122.
7. Marino J, English C, Caballero J, Harrington C. The role of paliperidone extended release for the treatment of bipolar disorder. *Neuropsychiatr Dis Treat*. 2012;8:181–189.
8. Huys D, Hardenacke K, Poppe P, Bartsch C, Baskin B, Kuhn J. Update on the role of antipsychotics in the treatment of Tourette syndrome. *Neuropsychiatr Dis Treat*. 2012;8:95–104.
9. Yilmaz A, Simsek F, Gonul AS. Reduced reward-related probability learning in schizophrenic patients. *Neuropsychiatr Dis Treat*. 2012;8: 27–34.