Introduction

A New Era in the Pharmacotherapy of Psychotic Disorders

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Schizophrenia and related psychotic disorders are debilitating illnesses affecting approximately 1% of the world population. These illnesses are generally chronic, beginning early in life and persisting into the elderly years. The impact of the illnesses on affected individuals and their families is monumental. The positive symptoms of schizophrenia lead to disruption of coherent thinking, anxiety, and distress that make day-to-day functioning challenging. The negative symptoms have a significant impact on social functioning, resulting in a lonely, isolated existence. Schizophrenia is associated with an alarmingly high suicide rate of 10% that speaks to the forlornness caused by the illness.[1] Comorbid depression is common and often untreated[2] and is a contributing factor to the high suicide rate associated with schizophrenia. Primary cognitive deficits affecting memory and attention are pervasive and cause work and social dysfunction such that it is uncommon for individuals with schizophrenia to hold gainful employment and lead independent lives. Relapse, an all-too-common feature of the illness, can lead to hospitalization, which disrupts community-based activities and contributes to substantial costs. It is clear that schizophrenia is the most severe psychiatric disorder and stands as a major public health issue.

Perhaps the most clinically meaningful and important scientific discovery in schizophrenia research over the past 40 years is the atypical antipsychotic agents. This group of drugs includes clozapine, risperidone, olanzapine, and quetiapine, with the possibility of at least 3 more new atypical drugs expected in the market over the next few years. As a class, they offer efficacy that is at least comparable with the older conventional antipsychotic drugs and have the distinction of being associated with either no dose-dependent extrapyramidal side effects (EPS) (clozapine, olanzapine, quetiapine) or reduced EPS (risperidone) compared with conventional agents. Because of their superior profiles and the substantial unmet need associated with this illness, the atypicals are rapidly replacing conventional agents for nearly all schizophrenia subgroups, namely, first-episode, treatment-resistant, partially responding, relapsing, and stable-but-chronic patients.

It is useful to emphasize that although the atypicals as a group differ from the older typical neuroleptics, there are quite marked differences among the atypicals, such that each atypical must be evaluated on its own merits as a distinct entity. Their neurochemical profiles show dramatic differences. While all atypicals have a higher serotonin-2A ($5\text{-}HT_{2A}$) to dopamine-2 (D_2) binding ratio compared with conventional agents (a feature that has been hypothesized to account for their "atypicality"), the degree of D_2 binding varies quite substantially; risperidone has the greatest degree of D_2 binding, possibly accounting for the dose-dependent EPS observed with this agent. In addition, head-to-head trials among the atypicals are revealing marked differences in safety and efficacy. Thus, each atypical antipsychotic must be evaluated on its own merits on the basis of the quality of clinical trial data available.

The most important criterion for evaluating a new antipsychotic treatment is efficacy, followed by safety. Several atypical antipsychotic drugs have superior efficacy for negative symptoms and cognitive impairment compared with traditional agents. While these effects are extremely important and greatly contribute to restoring functioning and quality of life, perhaps the most important domain in establishing efficacy of a new agent is its effects on positive symptoms. Positive symptoms, or psychosis, are the core and defining features of schizophrenia. To date, there is not overwhelming evidence that atypical antipsychotic agents have better efficacy for positive symptoms compared with traditional neuroleptics, with the exception of clozapine in treatment-resistant patients and, as reported in this supplement, olanzapine. Another area of paramount importance is the treatment of psychotic patients who are acutely agitated. Acute psychotic agitation can result in harm to patients and others. This clinical state demands that agents work quickly to quell the overt signs of agitation, without excessive sedation, and begin resolution of the accompanying florid psychotic symptoms.

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Safety is another key dimension for evaluating new antipsychotic therapies. As noted above, the older agents were marked by EPS and tardive dyskinesia. Minimal or no EPS are the most salient defining clinical features of the newer atypicals that have significantly contributed to their widespread adoption. Other safety concerns, however, have gained renewed attention with the atypicals. Cardiac safety, particularly conduction deficits involving repolarization and assessed with the QT interval, is of grave concern because prolongation of the QT interval may result in sudden unexpected death (SUD). Sertindole was the first marketed atypical that substantially prolongs QT interval (approximately 20 ms). In postmarketing experience, a number of SUDs occurred with its use, leading to the removal of sertindole from the market. Another atypical, ziprasidone, was not approved for use by the U.S. Food and Drug Administration (FDA) because of QT prolongation that is comparable with that seen with sertindole. Ziprasidone has been resubmitted for regulatory review and, at the time of this writing, a final regulatory action is still pending. While not as serious as QT prolongation and possible SUD, another issue related to antipsychotic agents that has heightened focus recently is weight gain. All antipsychotic agents are associated with weight gain, with the atypical agents being associated with more weight gain as a class than the traditional neuroleptics. The mechanism of antipsychotic drug–related weight gain is not known, although histamine-1 receptor antagonism has been hypothesized to be involved.

Olanzapine was introduced in late 1996 and has rapidly become one of the most prescribed atypical antipsychotic agents throughout the world, with over 5 million patients treated to date. Its neuropharmacology is quite varied, with a higher 5-HT_{2A} to D_2 binding ratio in addition to effects at other dopamine and serotonin receptor subtypes and other neuroreceptors. Olanzapine potently causes enhanced release of dopamine and norepinephrine in the prefrontal cortex,[3] an effect not shared by traditional neuroleptics or risperidone, which may account for its efficacy for cognitive impairment[4] and affective symptoms.[5–7] In addition, it antagonizes phencyclidine hydrochloride–induced disruption of normal information gating, suggesting important effects on glutamatergic neurotransmission; this antagonism is another possible mechanism for cognitive enhancement.[8] This effect is not observed with the older neuroleptics or risperidone. In addition to the well-characterized therapeutic benefits of olanzapine in schizophrenia, it is also effective for acute mania and associated depressive symptoms occurring in bipolar mania.[7] Olanzapine is the only antipsychotic agent with a formal FDA indication for acute mania.

This supplement is particularly noteworthy and timely because it presents new data about the efficacy and safety of olanzapine. In a large subset analysis of patients with schizophrenia, Gomez and Crawford report that olanzapine is superior to haloperidol for positive symptoms. The article by Karagianis and associates is interesting because it presents the first data examining a starting dose of 20 mg/day of olanzapine in acutely agitated patients. Previously, a starting dose of 10 mg/day was most commonly employed, but this pilot study indicated that 20 mg/day is well tolerated and may be the preferred regimen for the short-term management of acutely agitated psychotic patients, with a return to lower doses for maintenance treatment once the acute phase is controlled. Additional information about the role of olanzapine is contained in the article by Kinon and colleagues. The short-term effects of olanzapine on agitation and positive symptoms were compared with those of haloperidol. Both agents were equally effective over the first 3 weeks of treatment. This finding is of interest because haloperidol is commonly considered a "gold standard" treatment for acute agitation. Over the next 3 weeks, olanzapine demonstrated superiority to haloperidol. In a subset of patients with high baseline positive symptoms, olanzapine was superior to haloperidol for positive symptoms. A third article that provides new insights into the role of olanzapine in acutely agitated psychotic patients is by Jones et al. This article contains new data about a novel, short-acting, intramuscular olanzapine formulation. Decreases in agitation occurred quite rapidly, with clinically meaningful tranquilization occurring within hours of administration and similarly rapid reductions in positive symptoms. These data, together with the 20-mg initial dose data, indicate that olanzapine has a rapid onset of action and is an effective treatment for psychotic patients, providing that appropriate doses are used.

Two additional efficacy articles that provide new information about olanzapine are from Martényi et al. and Dossenbach et al. The first article demonstrates olanzapine's effectiveness in treating patients suffering from catatonia. If confirmed, these data are important, because acute catatonia can pose a psychiatric emergency and is often refractory to other pharmacologic interventions. The Dossenbach et al. article demonstrates that olanzapine is a good treatment option for patients who are nonresponsive to risperidone. This study underscores the fact that the atypicals are quite different from each other in terms of patient responsiveness and symptom amelioration. Czekalla provides a scholarly review of cardiac effects of antipsychotics, with a special focus on the QT interval. Lastly, the article by Jones and associates contains a review of olanzapine-related weight changes. Of note is the fact that weight gain plateaus relatively early in the course of treatment and olanzapine weight change is predicted by low baseline body mass index, reports of increased appetite, and good clinical response.

The advent of the atypical antipsychotic agents has initiated a new chapter in the treatment of schizophrenia and related disorders. As evidenced by this supplement, the clear beneficiaries of this new pharmacotherapy of schizophrenia are the millions of patients afflicted with this disease.

REFERENCES

1. Breier A, Astrachan BM. Characterization of schizophrenic patients who commit suicide. Am J Psychiatry 1984;141:206–209
2. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998;55:250–258
3. Li XM, Perry KW, Wong DT, et al. Olanzapine increases in vivo dopamine and norepinephrine release in rat prefrontal cortex, nucleus accumbens and striatum. Psychopharmacology (Berl) 1998;136:153–161
4. Purdon SE, Jones BD, Stip E, et al, and the Canadian Collaborative Group for Research in Schizophrenia. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. Arch Gen Psychiatry 2000;57:249–258
5. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
6. Tohen M, Sanger TM, McElroy SL, et al, and the Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. Am J Psychiatry 1999;156:702–709
7. Tohen M, Jacobs TG, Grundy SL, et al, and the HGGW study group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2000;57:841–849
8. Bakshi VP, Geyer MA. Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic olanzapine. Psychopharmacology (Berl) 1995;122:198–201