From Chlorpromazine to Olanzapine: A Brief History of Antipsychotics

Jonathan M. Meyer, M.D.
George M. Simpson, M.D.

The introduction of chlorpromazine in the 1950s had a profound impact on psychiatric practice throughout the world. Apart from the convulsive therapies, which were complicated, unaesthetic, and costly, treatment of patients with chronic psychotic disorders consisted of nonspecific sedation, restraint for agitation, and psychosocial interventions that varied from mildly beneficial to outright silly. The extant programs and clinics mostly offered psychodynamic psychotherapy, which proved generally unhelpful as a specific treatment for psychosis (1).

The reports from France in 1952 about the beneficial effects of chlorpromazine, a drug synthesized for use in anesthesia, on psychotic disorders such as schizophrenia forever changed the outlook on treatment of chronic psychoses. For the first time, an oral agent was available that predictably relieved the positive symptoms of schizophrenia, including delusions, hallucinations, and disorganized thoughts or behavior, among 70 percent of patients (2).

During the early years of use, two classes of side effects were noted among patients receiving chlorpromazine. One group of side effects was relatively benign and related to the drug's ability to block three types of receptors—histamine H_1 receptors, resulting in sedation and weight gain; adrenergic alpha$_1$ receptors, resulting in orthostatic hypotension; and muscarinic cholinergic receptors, resulting in dry mouth, tachycardia, constipation, and blurred vision. Although these side effects were a nuisance, patients often developed physiologic tolerance after continued administration of the medication.

Another group of side effects usually appeared in the first days to weeks of treatment and involved the extrapyramidal motor system, resulting in acute dystonic reactions; akathisia, or restlessness; and Parkinson's syndrome, involving tremor, slowed movements, and rigidity. Tardive dyskinesia was later noted among about 20 percent of patients on chronic chlorpromazine therapy; it was most often clinically characterized by involuntary abnormal movements of the lips, tongue, and digits and, rarely, of the trunk and extremities. In some individuals these symptoms did not remit on discontinuation of the drug (3).

Although the constellation of extrapyramidal side effects was related to the blockade of dopamine D_2 receptors in the basal ganglia, this pharmacologic property of D_2 blockade also appeared to be responsible for the therapeutic effects of chlorpromazine within the cerebral cortex. Despite the side effects, most patients responded to the medication with a reduction in positive symptoms, and the dopamine model of psychosis led to development of dozens of antipsychotics sharing in common their relatively potent ability to block D_2 receptors.

These typical antipsychotic drugs, however, seemed to exert a negligible effect on the negative symptoms of schizophrenia, such as apathy, avolition, flattening of affect, and alogia (4). Nevertheless, control of the more florid psychotic symptoms allowed for the discharge of large numbers of patients from state hospitals, unfortunately into community systems ill prepared and ill equipped for the necessary follow-up and treatment of chronic mentally ill patients.

From a pharmacological point of view, the arrival of clozapine revolutionized the outlook on schizophrenia treatment much as did the release of chlorpromazine years earlier. Synthesized in 1958 in Bern, Switzerland, clozapine is a dibenzodiazepine compound structurally derived from tricyclic models. In the laboratory it was noted to lack the classic antipsychotic effects on repetitive behavior in animals given amphetamines, properties that are dependent on a high level of D_2 blockade.

Clinical trials involving patients with schizophrenia showed that clozapine was an extremely effective antipsychotic and that it was not associated with the extrapyramidal symptoms seen with typical antipsychotics. This unique property of controlling psychosis without inducing extrapyramidal symptoms demonstrated to psychopharmacologists that the clinical effect of an antipsychotic could be separated from its liability to cause such side effects (5).

The other distinguishing characteristic of clozapine is its ability to ameliorate the negative symptoms of schizophrenia. Whereas all typical

Dr. Meyer is a fellow in the division of consultation-liaison psychiatry in the department of psychiatry and the behavioral sciences at the University of Southern California School of Medicine, 1937 Hospital Place, GRH 240, Los Angeles, California 90033. Dr. Simpson, the editor of this column, is professor of research psychiatry and director of clinical research in the department of psychiatry and the behavioral sciences at the University of Southern California School of Medicine.

antipsychotics were equally effective in controlling the positive symptoms of schizophrenia, about 30 percent of patients did not respond significantly to these agents, and they had little impact on the disabling cluster of negative symptoms. Thus clozapine was unique in its ability to treat negative symptoms and in the lack of extrapyramidal symptoms associated with therapeutic dosages (6). Clozapine quickly established itself as the therapeutic gold standard by achieving response rates of 30 to 61 percent in various studies among patients with schizophrenia who were refractory to previous treatment with typical antipsychotics.

Due to concern that clozapine could cause a potentially fatal side effect involving reduced white blood cell counts, clozapine was not released in the United States until 1990, and it is distributed only in association with weekly monitoring of patients' white blood cell count (7). Clozapine also possesses antihistaminic and anticholinergic side effects and may cause orthostatic hypotension and seizures (8,9). Dose titration is often slow in an attempt to limit side effects. Patients are typically started on 25 mg a day, and doses are increased up to the therapeutic range of 300 to 900 mg a day over several weeks.

Despite its unfavorable side effect profile, clozapine became the model for a new class of so-called atypical antipsychotics that were to share the pharmacologic combination of potent postsynaptic serotonin 5-HT_2 receptor blockade with D_2 binding that was weaker than that of typical antipsychotics, while avoiding the adverse effects associated with clozapine (10,11). Thirty years after the synthesis of clozapine, risperidone, the first atypical antipsychotic modeled on these pharmacologic properties, was created (12). Risperidone lacks clozapine's effects on the bone marrow, blocks postsynaptic 5-HT_2 receptors, and has weaker affinity for D_2 receptors compared with typical antipsychotics; however, extrapyramidal symptoms became evident among patients whose dosages were increased above 8 mg a day (13,14).

Several other similarly designed drugs are still in clinical trials. The newest atypical antipsychotic currently available is olanzapine, released in the United States in the fall of 1996. Pharmacologic data from in vitro laboratory studies and binding studies using positron emission scans predicted a profile of potent 5-HT_2 blockade and low D_2 receptor occupancy similar to that of clozapine (15,16).

Olanzapine also shares clozapine's inhibition of histaminic and cholinergic receptors, but the clinical effect of this action is not as prominent as that associated with clozapine. Whereas clozapine is a low-potency agent, active in the range of 300 to 900 mg a day, olanzapine appears effective in treatment of schizophrenia at much lower doses—5 to 25 mg a day—a property that may help minimize sedation. Of interest is that olanzapine is a 40-fold more potent inhibitor of $alpha_2$ adrenergic receptors than clozapine, but the clinical significance of this property is not yet known.

In an international double-blind placebo-controlled study involving 1,996 patients, olanzapine was superior to haloperidol on several outcome measures after six weeks (17). The olanzapine group had greater reductions in mean scores on the Brief Psychiatric Rating Scale (BPRS) ($p<.02$), and significantly fewer patients in that group dropped out of the trial due to lack of efficacy ($p<.001$) or adverse affects ($p<.01$).

Specifically, the incidence of extrapyramidal symptoms was markedly less with olanzapine for measures of dystonia, akathisia, and parkinsonism ($p<.001$). The olanzapine group reported slightly more complaints of dry mouth and increased appetite than did the haloperidol group. In another placebo-controlled trial of olanzapine among patients with schizophrenia, the incidence of extrapyramidal symptoms among patients receiving olanzapine was comparable to that for patients receiving placebo, and efficacy was noted at a dosage of 10 mg a day (18). Olanzapine also demonstrated superior effectiveness compared with haloperidol in the treatment of negative symptoms in a 52-week double-blind placebo-controlled trial involving 355 persons with schizophrenia (19).

A preliminary report on a head-to-head comparison of risperidone and olanzapine was reported at the December 1996 meeting of the American College of Neuropsychopharmacology (20). This interim analysis involved a total of 297 patients who met *DSM-IV* criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder and who were randomly assigned to receive either olanzapine (10 to 20 mg a day) or risperidone (4 to 12 mg a day) in an eight-week acute-phase trial with a 20-week maintenance extension phase. Patients who were randomly assigned to receive olanzapine were started at 15 mg a day to enhance the likelihood of associated adverse effects and thereby to remove potential bias in comparing the two drugs. Mean dosages at the end of the acute phase were 17.1 mg a day of olanzapine and 7.3 mg a day of risperidone.

During the acute phase, the olanzapine group was numerically superior in BPRS and total Positive and Negative Symptom Scale (PANSS) scores, with statistically significant superiority in the PANSS mood subscore ($p<.003$). This effect was also demonstrated at the end of the 28-week extension phase ($p<.001$). Notably, no patients in the olanzapine group had developed extrapyramidal symptoms by eight weeks, compared with 6.8 percent of the patients in the risperidone group; the incidence of extrapyramidal symptoms, as measured by Simpson-Angus ratings, was 10.4 percent in the olanzapine group and 21.1 percent in the risperidone group at the end of 28 weeks. The mean dosages at the conclusion of the study were 17.1 mg a day for olanzapine and 7.3 mg a day for risperidone.

Although more head-to-head comparisons are necessary, it would appear that olanzapine is an effective agent with a low propensity for extrapyramidal symptoms. It can be started at a dosage of 10 mg a day, which appears to be therapeutic for the majority of patients. This rapid dose titration confers a possible advantage over the other currently available atypical drugs, especially

clozapine. While we wait for further trials, it is safe to say that olanzapine represents a welcome addition to the therapeutic armamentarium for the psychoses. ♦

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