Antipsychotic Dosing: Extended, and Transient

Philip Seeman [1], Gary Remington [1, 2, 3]

New Ways of Antipsychotic Dosing

Considering the few new medications being developed for schizophrenia, it is recognized that novel avenues of research are needed for drug treatment of schizophrenia. While current antipsychotic drugs primarily block dopamine D2 receptors or interfere with dopamine neurotransmission (1, 2), many drugs for non-D2 pathways and receptors have been tested as possible antipsychotics, but not with much success. These include antagonists or agonists at receptors for D1 (SCH 23390), D3 (BP897; ABT925), D4 (fananserin/sonepiprazole), cannabinoids (rimonabant), neurokinins (SR142801; osanetant), neurotensin (SR48692), glycine transport inhibitors, ampakines (CX516), and serotonin (MDL100907; SR 46349B). The hypoglutamate hypothesis of schizophrenia suggests that low stimulation of glutamate receptors may be a basis for the illness. In fact, Patil et al. (3) reported that activation of the metabotropic glutamate-2/3 receptors (mGluR2/3) by LY404039 (or its precursor, LY2140023) was clinically equi-effective as olanzapine in alleviating psychotic signs and symptoms of patients with schizophrenia. Recently, however, Kinon et al. (4) reported that the clinical efficacy of LY404039 was "inconclusive."

At present, therefore, it appears that at least a D2-blocking component is needed for the treatment of schizophrenia.

[1]Department of Pharmacology, University of Toronto
[2]Department of Psychiatry, University of Toronto
[3]Centre for Addiction and Mental Health, Toronto

Address for correspondence: Philip Seeman, MD, PhD, Pharmacology Department, University of Toronto, 260 Heath Street West, Unit 605, Toronto, Ontario, Canada M5P 3L6
E-mail: Philip.Seeman@utoronto.ca

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In addition, while there is preclinical information in animals that stimulation of mGluR2/3 receptors might be therapeutic, the clinical efficacy of this approach has not yet been clearly established (4).

While interference with dopamine transmission at D2 is the minimum drug requirement for treating schizophrenia, there are new ways and new drugs that optimize the dosing of patients to minimize side effects and rehospitalization. These new ways are based on the fact that some antipsychotics, such as clozapine, quetiapine, amisulpride, remoxipride and amoxapine, attach to the D2 receptor *in vitro* for brief periods of time (half-times of 15 to 66 seconds) before dissociating from the D2 receptors (5-7). In fact, the transient attachment (a few hours *in vivo*) of quetiapine to D2 has been confirmed in patients (8).

Extended Dosing for Tightly D2-Bound Antipsychotics

Other antipsychotics, such as haloperidol, chlorpromazine, loxapine and olanzapine, stay attached to D2 receptors for much longer periods of time *in vitro* (15 to 30 minutes; [5-7]). The long-term occupation of D2 receptors (over 72 hours) by a single dose of haloperidol in patients has been confirmed by positron tomography (9).

Because of the prolonged attachment of haloperidol, risperidone and olanzapine to D2 receptors in humans, it was considered reasonable and clinically safe to orally dose schizophrenia outpatients once every second day (10, 11). Such "extended" dosing reduced rehospitalizations from 22% (4/18 regularly treated subjects) down to 6% (1/17 alternate-day-treated subjects), while slightly reducing the BPRS ratings and showing no increase in extrapyramidal signs (11).

While extended alternate-day treatment of haloperidol, risperidone or olanzapine would considerably reduce the

lifetime drug accumulation that increases the risk of tardive dyskinesia (12, 13), it is uncertain whether outpatients can conveniently remember to take alternate-day medication. If they can, drug costs would be halved. It is important to emphasize that extended alternate-day treatment is not the same as prolonged nonadherence to the medication. In addition, it is important for the clinician to watch for any possible acute relapse in patients taking "extended" dosing, although such acute relapse was not observed in the patients studied by Remington et al. (10, 11).

Transiently D2-Acting Antipsychotics

A second new strategy to minimize side effects and risk of tardive dyskinesia is to use antipsychotics such as clozapine or quetiapine that are rapidly released from the D2 receptor (5, 8). However, clozapine requires white blood cell monitoring and causes weight gain, while quetiapine also causes weight gain. Both drugs increase the risk of diabetes and cardiovascular disease.

No new antipsychotics based on the "fast-off-D2" principle (5, 6) have emerged until recently (14). Johnson & Johnson reported that its new fast-off-D2 drug (JNJ-37822681) was given at 30 mg BID, occupied 65% or more of the D2 receptors in patients for only 10% of the dosing interval, caused only a transient elevation in prolactin, caused no increase in body weight or extrapyramidal signs, and reduced the clinical PANSS rating by 20 points within 6 weeks (14).

The remarkable aspect of the fast-off-D2 drugs of clozapine, quetiapine and the JNJ compound is that they occupy D2 receptors for only a few hours, yet the patients do not experience psychotic symptoms the following morning when the D2 receptors are far less occupied. It is important to note, however, that while clozapine and quetiapine are both fast-off-D2 drugs, quetiapine may not be as clinically effective as clozapine, especially if quetiapine is given in divided doses (BID regimen) that tend to limit the attainment of an optimum occupancy of at least 60% of D2 receptors. Moreover, receptors other than D2 may assist in the main clinical action of clozapine on D2 receptors.

While the extended dosing regimen assumes that the D2 receptors remain occupied for days, the transient drug regimen suggests that the continued 24-hour high occupation of D2 receptors may not be essential for antipsychotic efficacy. The success of extended dosing may depend on this fact.

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Philip Seeman has recently received speaker fees from Sunovion, and is associated with Clera Inc. Over the last three years, Gary Remington has received research support from Novartis Pharmaceuticals Canada Inc., Medicure Inc., and Neurocrine Biosciences. He has also received speaker fees from Novartis Pharmaceuticals Canada Inc. He has no pharmaceutical industry stock holdings.

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