Dear Editor:

Dr. Seeman’s hypothesis with regard to the mechanism by which the atypical antipsychotics (APs) improve psychosis with a “minimum” of extrapyramidal side effects (EPSEs) is thought-provoking (1). Nevertheless, important observations remain unexplained. For example, according to this hypothesis, amoxapine should be atypical; however, it is not—at least, not in Parkinson’s disease (PD) patients (2). Pimozide, which is most similar clinically to haloperidol in terms of EPSEs, should in theory be more atypical than risperidone. Olanzapine, which certainly worsens parkinsonism in PD patients (thus illustrating its toxicity), has very little effect on prolactin levels, in contrast to risperidone and the typicals. According to their D2 binding, molindone and loxapine should be more atypical than risperidone. Olanzapine, which certainly worsens parkinsonism more atypical than risperidone. Olanzapine should be more atypical than risperidone. Olanzapine has potent antitremor effects in PD patients, and it works in patients who failed to respond to anticholinergics at higher dosages.

It is also apparent that formulating hypotheses is limited by conflicting data on just what motor side effects these drugs have.

I close by asking about the relevance of data suggesting preferential binding of drugs in and out of the striatum.

References

Joseph H Friedman, MD
Pawtucket, Rhode Island

Reply: Atypical Antipsychotics
Mechanisms of Action

Dear Editor:

The basic principle proposed in my article (1) is that there are 2 groups of antipsychotics (APs), those that bind tightly to the dopamine D2 receptor and those that bind more loosely to the D2 receptor (2–4). The traditional APs, which elicit parkinsonism, bind to the dopamine D2 receptor more tightly than does dopamine to the high-affinity state of the D2 receptor. The newer, atypical APs, which elicit less or no parkinsonism, bind to the dopamine D2 receptor more loosely than does dopamine to the high-affinity state of the D2 receptor (1).

I am also aware that formulating hypotheses is limited by conflicting data on just what motor side effects these drugs have.

I close by asking about the relevance of data suggesting preferential binding of drugs in and out of the striatum.

References

Joseph H Friedman, MD
Pawtucket, Rhode Island
atypical APs, especially when discussing the action of APs for L-DOPA psychosis in Parkinson’s disease patients, as Dr Friedman properly points out. For example, Dr Friedman notes that amoxapine, with its high dissociation constant of 20 nM (1), ought to be an atypical AP—as in fact it is for patients with schizophrenia (S Kapur, personal communication, 1999), but not for patients with Parkinson’s disease (10). As outlined previously (1), the Parkinson putamen has only 2% or 3% of the normal amount of dopamine (11), and Parkinson’s disease patients with L-DOPA psychosis should in principle receive one-thirtieth the dosage of an atypical AP given to patients with schizophrenia. Because the recommended AP dosage of amoxapine is 150 to 250 mg daily (12), the starting dosage for Parkinson’s disease subjects ought, a priori, to be about 6 mg daily. However, the amoxapine starting dosage was 12.5 mg daily for the 3 patients tested by Sa and others (10). Although APs with dissociation constants between 2 and 20 nM can elicit dosage-dependent parkinsonism, the dissociation speed of the radio-labelled AP best predicts whether an AP will be atypical. While it has been directly determined that [3H]clozapine, [3H]-S- amisulpride and [3H]quetiapine are the APs most rapidly released from the D2 receptor (1), [3H]amoxapine is not available for such studies.

It is not especially surprising that amoxapine avoids eliciting extrapyramidal signs in schizophrenia patients but intensifies such signs in Parkinson’s disease patients, because other atypical APs, such as olanzapine and risperidone, also worsen parkinsonism in this patient group, as noted by Dr Friedman and others (13,14). It appears, therefore, that APs with dissociation constants between 2 nM and 20 nM can be atypical in patients with schizophrenia, but not in patients with Parkinson’s disease, while APs with dissociation constants above 20 nM (that is, clozapine, quetiapine, and melperone) are atypical in both diseases. The different ranges correspond to the different levels of endogenous dopamine, which is high in schizophrenia but very low in Parkinson’s disease.

As for pimozide, there is no reason to expect it to be more atypical than risperidone, because their dissociation constants are virtually identical (1). Concerning olanzapine, this drug does elevate prolactin (15,16). However, while atypical APs avoid EPSs, their propensity to elevate prolactin differs, depending on their fat solubility (17). Hence, risperidone, with high fat solubility and high affinity for the pituitary D2 receptor, readily elevates prolactin. Conversely, quetiapine, with low fat solubility and low affinity for D2, has little effect on prolactin.

Molindone and loxapine have dissociation constants in the range of 2 nM to 20 nM for D2 and thus elicit dosage-dependent parkinsonism (1). As for thioridazine, this compound has repeatedly been observed to cause fewer EPSs (18,19). Concerning the anticholinergic effects of thioridazine and clozapine, these drugs have the same potent affinity as benztropine for the M1 muscarinic-cholinergic receptor (that is, dissociation constants of 3 nM) (20,21). Hence, clinical dosages of 200 to 400 mg daily of clozapine or thioridazine are equivalent to giving a patient one hundredfold more of the customary benztpine dosage of 2 mg twice daily. It is not surprising, therefore, that clozapine would be clinically more effective than benztpine in alleviating parkinsonism. As for the absence of systemic side effects with clozapine (that is, dry mouth and blurred vision, although clozapine does cause constipation), it is known that clozapine is a potent agonist at the M4 muscarinic receptor (22). This agonist action may underly clozapine-induced hypersalivation and the absence of systemic anticholinergic effects. In addition, because clozapine has a tenfold range of different affinities for the 5 different muscarinic receptors (21,22), the receptor basis for the clinical cholinergic and anticholinergic actions of clozapine is not obvious.

On the question of relevance of data for drugs binding in and out of the striatum, the D2 percentage occupancy by a drug in the striatum is generally identical to, or slightly lower than, the D2 occupancy for nonstriatal brain regions, such as the cingulate cortex (23,24). Hence, data for the striatum can be generalized to other brain regions. However, the data for the speed of dissociation of [3H]APs from the human cloned dopamine D2 receptor (1) are obtained under artificial optimum laboratory conditions and, therefore, only reflect the principles under study.

In summary, Dr Friedman is correct to point out that each atypical AP has unique properties in addition to whether each has tight or loose binding to the D2 receptor. We can conclude that APs that are atypical for schizophrenia patients may not be sufficiently loosely bound to D2 to be atypical for Parkinson’s disease patients. Clearly, APs must be extremely loosely bound to D2 (as is the case with clozapine or quetiapine) to effectively treat L-DOPA psychosis in dopamine-depleted Parkinson’s disease patients, without enhancing their tremor, akinesia, and rigidity.

References
2. Seeman P, Tallerico T. Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. Mol Psychiatry 1998;3:121–34.
siently high dopamine D2 receptor occupancy. Arch Gen Psychiatry 2000;57:553–9.
7. Kapur S, Seeman P, Zipursky R, Remington GJ. Fast dissociation from the dopamine D2 receptor (not high affinity at multiple receptors) is the key to atypical antipsychotics. Schizophr Res 2001;49(1,2 Suppl):S22.

Philip Seeman, MD, PhD
Toronto, Ontario

Re: “Cades Disease” and Beyond

Dear Editor:

Dr Ghaemi and colleagues are convinced that bipolar disorder (BD) is greatly undiagnosed (1).

Recently, I have seen 2 cases in which patients were diagnosed and treated for BD after being treated for other diagnosed disorders. In each case, their conditions worsened.

Case Report 1

Mrs A is married, in early middle age, and has 2 teenage children. She was admitted to hospital and diagnosed with unipolar depression, together with some long-standing personality and family problems. She responded poorly to treatment, was discharged with mild improvement, and readmitted soon after. On readmission, her treating psychiatrist undertook a detailed review of her history, rediagnosed her with BD, and treated her with divalproex. She was told the diagnosis. She seemed to improve rapidly, and was discharged home. In follow-up for the next few months, her self-report was very good and she was very pleased with the psychiatrist for taking the time to reassess her and find the “correct” diagnosis. Then, one of her daughters attempted suicide, giving as a reason the fact that her mother had no time for her because she was spending all her time on a BD Internet chat line. After this, the patient was no longer pleased with her psychiatrist and was lost to follow-up.

Case Report 2

When she presented for treatment, Mrs B, also middle-aged, was in a second, quite supportive marriage. She had a history of an abusive first marriage and severe dysfunction during her childhood. She had left that marriage, taken a college course that interested her, obtained a diploma, and obtained appropriate work. She quickly found her work too stressful, largely because it reminded her of things in her past that caused a recurrence of posttraumatic stress disorder (PTSD) symptoms. When she presented for treatment, she was diagnosed with unipolar depression, generalized anxiety disorder, and subsyndromal PTSD symptoms. She did not respond well to treatment and was unable to return to work after a period of many months. She and her husband then decided to seek assessment and treatment from a different psychiatrist, with the original psychiatrist’s agreement. She was diagnosed with BD, started on divalproex, and discharged. A few months later, she presented to her original psychiatrist. She said that on divalproex she had felt “totally flat” and refused to live that way. She had therefore discontinued it, and her former symptoms all promptly recurred. Her psychiatrist told her that he did not agree with the diagnosis of BD but had no new treatment to offer her, other than a trial of different antidepressant medication. She accepted that and also learned to accept that she was not able to work in her chosen field. She subsequently improved moderately.

I suggest that there may be as much danger in overdiagnosing as in underdiagnosing BD.

Reference


EJ Wiebe, MD, FRCPC
Edmonton, Alberta

Reply: Cade’s Disease and Beyond

Dear Editor:

Dr Wiebe describes 2 cases that in our opinion fail to indicate that bipolar disorder (BD) is overdiagnosed. In the first case, a patient was diagnosed with BD
and spent a great deal of time on Internet chat sites, to the dismay of her family. This activity does not speak at all to the question of whether the BD diagnosis was accurate. In the second case, the patient was diagnosed with BD and did not feel that valproate helped her. Again, this fact by itself does not prove that the BD diagnosis was inaccurate. Indeed, response to a single mood stabilizer occurs, at best, in only one-third of patients with BD (1). Many patients with BD who respond to lithium do not respond to valproate, and vice versa (2). The correspondent’s complaint in the second case appears chiefly to be about the treatments for BD and not about the diagnosis itself. It is our sense that many clinicians hesitate to diagnose BD because of their dissatisfaction with available treatments. This is a practical problem; hopefully, it will be less of an issue as newer, more tolerable mood stabilizers are developed. However, this practical problem has nothing to do with the empirical fact of whether someone meets or does not meet criteria for BD, based on an accurate and complete examination of symptoms and history. It is also interesting that both patients apparently responded poorly to standard unipolar treatments (antidepressants), yet the author does not conclude that this argues against the unipolar diagnosis. In fact, poor outcomes with antidepressants are quite common in the histories of patients with BD, as we reviewed in our paper. Plenty of evidence to the contrary—that BD has been and remains underdiagnosed. Even if occasional cases of erroneous diagnosis were found, it would be necessary to show that such cases are more frequent than the misdiagnosis of BD before one could claim that BD overall is overdiagnosed. It is a simple fact of scientific method, highlighted by the evidence-based medicine literature (3), that case reports do not refute empirical studies. There is no appreciable evidence that BD is overdiagnosed.

References


S Nassir Ghaemi, MD
James Y Ko, AB
Frederick K Goodwin, MD
Cambridge, Massachusetts

Quetiapine-Induced Leucopenia: Possible Dosage-Related Phenomenon

Dear Editor:

Quetiapine is as effective as haloperidol and chlorpromazine in relieving both the positive and negative symptoms of schizophrenia at dosages ranging from 150 to 750 mg daily (1–3).

In premarking placebo-controlled trials, quetiapine use has been associated with a dosage-related decrease in total and free thyroxin (T4), with transient leukopenia, and with an elevation from baseline in cholesterol, triglyceride, and hepatic transaminases (4).

Case Report

MM is a 41-year-old woman diagnosed with schizophrenia at age 22 years. While taking chlorpromazine 600 mg daily, she was well (that is, her schizophrenia was episodic, with no interepisode residual symptoms) and functioned independently in the community for over 18 years.

Nonadherence to treatment preceded the recurrence of positive symptoms, social withdrawal, and poor personal hygiene, which led to her readmission to a psychiatric hospital for over 7 months in 2001. Pharmacotherapy with optimal dosages of olanzapine and risperidone did not appreciably improve her target symptoms. After haloperidol 10 mg daily was commenced, improvement in the target symptoms was evident, and she was discharged home. She was readmitted 7 weeks later because she had not adhered to follow-up plans and had discontinued her medication without medical advice. After she developed extrapyramidal side effects (EPSs), haloperidol was replaced by quetiapine at 150 mg daily, titrated to 600 mg daily over 4 weeks, and the EPSs resolved. Her pre-quetiapine white blood cell count (WBC) was 6.6, and her absolute neutrophil count was 4.0. Four weeks later, a repeat complete blood count revealed leukopenia of 1.7 and absolute neutrophilia of 0.3. The following day, the leucocyte and absolute neutrophils counts were 2.0 and 0.2, respectively.

MM agreed to the substitution of chlorpromazine for quetiapine. She had no clinical evidence of infection, her vital signs were normal, and she had no known prior or contemporaneous medical history that might explain the laboratory findings. At quetiapine 450 mg daily, 300 mg daily, 150 mg daily, and 1 week after discontinuation, the respective WBC and absolute neutrophil counts were 2.4 and 0.4, 4.8 and 2.8, 6.2 and 4.6, 6.4 and 4.7 (within normal limits). MM refused a rechallenge with quetiapine. This patient experienced a quetiapine-associated, dosage-related, reversible leukopenia. Hematological abnormalities
have been reported with the use of atypical antipsychotic (AP) drugs, especially clozapine-induced agranulocytosis (5). The mechanism by which these drugs induce these abnormalities remains uncertain, but they could be immunologically mediated or caused by direct bone-marrow toxicity (6). Unlike clozapine, other atypical APs do not require adherence to a rigorous laboratory monitoring protocol. We consider it essential that physicians inform patients about the potential hematological abnormalities and educate patients about the signs and symptoms of reduced blood cell counts. Prudent clinical management also warrants routine WBC monitoring, at least during initiation of quetiapine and, possibly, other atypical APs. The possible absence of physical symptoms to alert both clinician and patient to immunologically compromise jeopardizes timely identification of potentially marked neutropenia. We also think an efficient and effective strategy is needed to identify hematologically compromised patients who are at high risk of developing medical complications associated with neutropenia, before they receive atypical antipsychotics.

References


Oluruntoba Oluboka, MBBS, FRCP
David Haslam, MD, MSc, FRCP
Treena Lam, MD, CCFP
Diane Bown-Demarco, RN

North Bay, Ontario

Atypical Neuroleptic Malignant Syndrome With Clozapine and Subsequent Haloperidol Treatment

Dear Editor:

Clozapine can cause neuroleptic malignant syndrome (NMS), with a presentation that may be atypical in that it may occur without rigidity, fever, or changes in creatine kinase (CK) (1). We report a patient who developed atypical NMS while taking clozapine, followed by a similar syndrome while taking haloperidol.

Mr A, aged 22 years, had a 5-year history of disorganized schizophrenia. He had previously failed trials of olanzapine, valproic acid, and risperidone. During an admission for exacerbated symptoms, a trial of clozapine was initiated. Prior to initiation, his white blood cell count (WBC) was slightly elevated, at 13.3 10^9/L. Neutrophils, blood pressure (BP), and heart rate (HR) were normal. The clozapine was started at 25 mg daily and titrated to 325 mg daily over 16 days, while his risperidone dosage of 5 mg daily was tapered off completely. Atypically, he had mild hypertension (maximum 156/96) on clozapine, which persisted. On day 17 of clozapine treatment, he declined his medication and was observed to be more disorganized. The following day, he vomited and was diaphoretic, agitated, and delirious, yet afibrile. He became more hypertensive and tachycardic, with marked elevations in his WBC (31.8 10^9/L), neutrophils (24.8 10^9/L), and CK (1442 IU/L). There was no rigidity or evidence of an infectious process. We discontinued the clozapine, and he received haloperidol 5 mg, and lorazepam 2 mg, daily. His WBC, neutrophils, BP, and HR all normalized within 24 hours. Over the following week, his delirium resolved and his CK dropped to 361 IU/L. After 5 days on haloperidol, his WBC, neutrophils, and CK suddenly rose again (17 10^9/L, 12.8 10^9/L, and 598 IU/L, respectively). He remained normotensive but became tachycardic. We discontinued haloperidol, and his vital signs and laboratory values subsequently normalized. Following a 1-week period of no antipsychotic (AP) treatment, Mr A was started on olanzapine without any further adverse effects.

To our knowledge, this is the first report of an atypical NMS occurring with clozapine and then repeated with another agent. It is possible that the return of this patient’s NMS symptoms might have been caused by residual clozapine in his system. However, the resolution of his laboratory abnormalities and symptoms, followed by their recurrence 5 days later, makes this unlikely. Certain individuals may be sensitive to clozapine and its low affinity for dopamine receptors (2), and this may underlie an incomplete NMS presentation. A multifactorial contribution from neurotransmitters may also explain the basis of atypical NMS (3). Haloperidol is a relatively specific dopamine blocker and the recurrence of NMS while Mr A was taking this medication lends more support to the dopaminergic theory. Nonetheless, this case highlights the possibility that patients taking clozapine may develop atypical NMS. Once NMS is present, subsequent AP medication should be introduced with caution.

References


Mitchell Spivak
Beverly Adams
David Crockford
Calgary, Alberta