Letters to the Editor

Need for a New Framework to Understand the Mechanism of All Antipsychotics

Sir: The advent of atypical neuroleptics has transformed the pharmacologic treatment of schizophrenia. The advent of single photon emission computed tomography (SPECT) and positron emission tomography (PET) neuroreceptor imaging makes it possible to link biochemical events in the human brain to their clinical consequences. Remington and Kapur[1] (supplement 10, 1999) have proposed an interesting model based on studies using PET that takes in account the serotonin-2/dopamine-2 ($5\text{-}HT_2/D_2$) occupancy threshold: conventional antipsychotics have low $5\text{-}HT_2$/high D_2 ratios, olanzapine and risperidone have high $5\text{-}HT_2$/high D_2 ratios, clozapine has a high $5\text{-}HT_2$/low D_2 ratio, and quetiapine has a low $5\text{-}HT_2$/low D_2 ratio.[2,3] Beyond 80% of D_2 blockade, extrapyramidal symptoms appear. To attain optimal blockade, 2 to 4 mg/day of a conventional neuroleptic such as haloperidol is sufficient. We agree that high doses of conventional neuroleptics are no longer favored.[4] This model is yet unable to explain 2 problems: the first is related to the efficacy on symptoms and the safety in terms of extrapyramidal symptoms (EPS) of the different substituted benzamides such as amisulpride, which has high potential for blocking D_2 and D_3 receptors and low potential for blocking $5\text{-}HT_2$ receptors.[5] The second is the absence of EPS with high D_2 occupancy related to high dosage of neuroleptics in some refractory patients.[6]

Only one substituted benzamide, remoxipride, has been sold in Canada and the United States, but it was withdrawn from the market because it was associated with the risk of developing aplastic anemia. Meanwhile, substituted benzamides (e.g., amisulpride, sultopride, sulpiride, tiapride) remain popular in Europe.[7,8] For example, amisulpride is effective against negative symptoms and associated with few EPS.[9–11] It is a benzamide derivative that has a high affinity for human dopamine D_3 and D_2 receptor subtypes. Its important action on D_3 receptors might account for some of its peculiarities. It has a very low affinity for $5\text{-}HT_2$ receptors. Therefore, it doesn't fit very well with Remington and Kapur's model despite several clinical trials showing good efficacy on symptoms and a low propensity of EPS.

The second problem is illustrated by the case of a schizophrenic patient who became resistant to 2 atypical neuroleptics but responded well to haloperidol in high doses.[6] Despite numerous therapeutic trials with various conventional neuroleptics in normal doses and mood stabilizers, the patient proved pharmacologically resistant. Atypical neuroleptics (risperidone and quetiapine) produced only a partial and temporary response. He refused clozapine. We then tried higher doses of haloperidol, increasing gradually from 20 mg twice daily to 25 mg 4 times daily. Over a period of 32 weeks, we saw his delusional thoughts disappear and his self-criticism improve. His Brief Psychiatric Rating Scale score decreased from 48 to 9. Only haloperidol in high doses has enabled the patient to attain functionality. Despite above-normal plasma levels of haloperidol, the patient has never presented with intrusive extrapyramidal side effects. Prolactin levels were high (115 mg/L; normal range, 12–30 mg/L). Attempts to reduce dosage below 80 mg/day resulted in relapse, with good recovery when dosage was restored.

A SPECT study was performed using a dual-headed camera and 185 MBq of 123-Iodobenzamide (IBZM). The specific-to-nonspecific binding ratio was measured at 90 minutes postinjection. The SPECT was performed a week after a PET analysis was kindly performed in Dr. Kapur's laboratory while the patient received 90 mg/day of haloperidol. No detectable receptors at this dosage were found with either technique.

Our findings lead us to wonder whether there exists a subgroup of chronic patients resistant to conventional and some atypical neuroleptics in normal doses, but who may respond well to conventional neuroleptics in high doses. Despite a high level of striatal D_2 occupancy, our patient did not present with EPS. We probably need a new framework to understand this antipsychotic inefficacy and good neurologic tolerability.

It has already been noticed that EPS may appear at relatively modest doses of haloperidol, for instance, and increase thereafter, but a megadose may make them vanish completely.[12] At the higher dose, an action on the noradrenergic system kicks in and seems to alleviate the EPS.[12] EPS can worsen on a lower dose and be alleviated by higher doses via concomitant manipulations of the noradrenergic system in this fashion.

Given this, our findings are not as surprising as we first thought. It would be a logical error to suggest an antipsychotic effect without entertaining the possibility that there may be a number of different antipsychotic therapeutic principles mediated through different receptor systems that come into play at different dose levels.

The model based on a $5\text{-}HT_2/D_2$ ratio is not sufficient to explain all the mechanisms of action of traditional and newer neuroleptics. First, schizophrenia is a heterogenous disease; second, the dopamine/serotonin systems are not the only pathway to be considered; and finally, the striatum is obviously not the only cerebral location implicated in the disease. It is a good model for the majority of patients with schizophrenia, but not for all the patients. It is a good framework for the majority of antipsychotics, but not for all compounds. It is very heuristically helpful and seems to be an incentive work in progress.

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Drs. Remington and Kapur Reply

Sir: We appreciate the comments by Stip and colleagues and would like to respond to several issues they have raised.

They suggest that the notion of D_2 occupancy thresholds for clinical response and extrapyramidal symptoms (EPS) (approximately 60% and 80%, respectively) does not adequately account for that group of individuals who require higher antipsychotic doses than what this model might predict. This is true. Certain individuals, albeit a small subgroup, appear to benefit from high-dose therapy,[1] reminding us that existing theories are not absolute.

They also note that there are patients taking high doses of antipsychotics who do not manifest EPS. We have suggested that increasing D_2 occupancy is associated with increased EPS; even the mitigating effects of concomitant 5-HT_2 antagonism can be overridden by high D_2 blockade. At the same time, high antipsychotic doses can paradoxically be associated with a diminished risk of EPS, suggesting a curvilinear rather than sigmoidal relationship between EPS and dose.[2] One explanation that can account for this phenomenon, at least in part, relates to increasing activity at other receptors, e.g., muscarinic, histaminic, as doses are raised.

Their report regarding substituted benzamides is an interesting one. It has been suggested that this group of compounds may have a diminished risk of EPS and a superior effect on negative symptoms compared with conventional antipsychotics, and Stip and colleagues postulate the role of other mechanisms, e.g., D_3, to account for this. However, a review of the clinical data may provide a more straightforward explanation. Looking at amisulpride, for example, it has been reported that doses of 630–910 mg/day are associated with D_2 occupancy in the range of 70% to 80%, below the identified threshold for increased risk of EPS. Trials with amisulpride have generally utilized doses of 800 mg or lower,[3,4] and studies reporting its efficacy in negative symptoms actually used much lower doses, i.e., 50–400 mg/day.[5–9] Moreover, studies have routinely used haloperidol as the comparative agent at doses well beyond current recommendations, e.g., ≥ 10 mg/day,[3,4] doses clearly associated with a high risk of EPS based on its D_2 occupancy profile.[10,11]

The model we have proposed addresses only dopamine and serotonin and is currently based solely on positron emission tomography (PET) evidence involving static equilibrium characteristics. Stip and colleagues refer to it as a "work in progress." They are absolutely correct.

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Atypical Antipsychotics for Treatment of Mixed Depression and Anxiety

Sir: Patients with chronic depression may respond poorly or not at all to antidepressant medications; those with comorbid anxiety or histories of traumatic stress may be especially difficult to treat. Standard antipsychotics have long been used by clinicians to treat high degrees of agitation and anxiety in nonpsychotic patients with severe personality disorders. The benefit these patients may derive is often judged to outweigh the risk of tardive dyskinesia.[1,2] The atypical antipsychotics used in conjunction with antidepressants have been reported effective in the treatment of nonpsychotic major depression.[3] Although the atypical antipsychotics are not indicated for treatment of anxiety, some nonpsychotic patients with mixed depression and anxiety may respond to these agents.

Three patients are described below, all seen in a university-affiliated outpatient practice. All 3 patients have been followed by the author for a minimum of 5 years, all have had DSM-IV recurrent unipolar major depression complicated by anxiety according to clinical interviews by the author (histories provided by previous treating psychiatrists confirmed this diagnosis in all

cases), and none have shown evidence of hypomania/mania or overt psychosis in clinical interviews at intervals of no less than 1 month.

Case 1. Mr. A, a 30-year-old male engineer with double depression (dysthymia and recurrent major depression), had experienced partial remission with imipramine, 300 mg/day, over 10 years. He had a history of significant childhood neglect and required several hospitalizations for depression as an adolescent and teenager. Mr. A had made steady gains with supportive psychotherapy combined with imipramine, 300 mg/day, such that he was able to finish his education and work at a level commensurate with his high intelligence and skill. Despite the improvement in his depression, Mr. A complained of continual anxiety, severe enough to interfere with sleep, concentration at work, and relationships. Selective serotonin reuptake inhibitors added to imipramine were not helpful, but he did experience good antidepressant effect with nefazodone, 600 mg at bedtime, and was able to discontinue imipramine. Still, he reported no improvement in his anxiety level. Benzodiazepines afforded partial relief, but he disliked the sedation and short duration of benefit associated with their use.

Mr. A had never been treated with antipsychotics in the past. Quetiapine, 25 mg at bedtime, led to a dramatic response within 1 week: after some initial sedation cleared, he experienced complete relief of the chronic anxiety. Mr. A noted that for the first time in memory he was able to feel relaxed without sedation, but also to experience "normal" anxiety, e.g., when thinking about going out on a date. This response has persisted for 6 months.

Case 2. Ms. B, a 47-year-old female lawyer, suffered significant childhood trauma and lifelong recurrent major depression, with hospitalization as a teenager and several episodes throughout adulthood variably responsive to antidepressant medication. She experienced a major depressive episode that had minimal response to SSRIs (fluoxetine, up to 80 mg/day for over 2 months; paroxetine, 60 mg/day for 6 weeks; sertraline, 300 mg/day for 6 months; fluvoxamine, 200 mg/day for 6 weeks; and citalopram, 40 mg/day, which she continues to take), monoamine oxidase inhibitors (phenelzine, 60 mg/day, led to incomplete response for 3 months and had to be discontinued owing to blurred vision that interfered with her work), venlafaxine (up to 150 mg of the extended-release formulation led to some improvement but unacceptable akathisia), bupropion (450 mg/day of slow-release form), or augmentation with thyroid hormone and mood stabilizers (valproate, lithium, carbamazepine, and topiramate). Ms. B was unable to interact with coworkers because of intolerable anxiety and self-deprecation that bordered on paranoia. Clonazepam and diazepam were tried without success.

Risperidone, 1 mg q.h.s., led to improvement in Ms. B's capacity to interact with coworkers, but no overt improvement in depression. Olanzapine, 2.5 mg q.h.s., led to a dramatic improvement within a few days in both depression and anxiety, with return of her productivity at work and her enjoyment of many social activities she had avoided while depressed. The initial response waned somewhat, but she remained euthymic when the olanzapine dose was increased to 10 mg/day. This increase led to weight gain of 25 pounds over a period of 3 months; although she was distressed by the weight gain, she was so impressed by the benefits of olanzapine that she has chosen to continue with 2.5 mg/day. She has had a sustained benefit for 10 months.

Case 3. Ms. C, a 55-year-old schoolteacher with significant childhood trauma, required disability status owing to severe recurrent major depression. She had no overt psychosis, but her anxiety and mild paranoia interfered with her capacity to take care of herself in that she avoided any activity that brought her into contact with other people. Ms. C had some antidepressant response with paroxetine, 60 mg/day, and bupropion, 450 mg/day, augmented with valproate, but even high doses of benzodiazepines were ineffective for her anxiety. Risperidone, 1 mg q.h.s., had a dramatic effect on her anxiety level within a few days of starting and led to a return of her willingness to shop for groceries and attend family gatherings. Ms. C has had sustained benefit for over 2 years. When she ran out of risperidone over a weekend, she was surprised at the intensity of the anxiety that recurred.

These cases demonstrate that, in patients with nonpsychotic recurrent and/or chronic major depression and high levels of anxiety, low doses of atypical antipsychotics may improve function through an antianxiety or antidepressant effect independent of their antipsychotic efficacy. Efficacy has been reported for atypical antipsychotics in affective illness and obsessive-compulsive disorder[4,5] and speculation has been made that their potent serotonin receptor antagonism, rather than dopamine blockade, leads to improvement in symptoms of anxiety and depression. This effect may occur with typical antipsychotics as well,[6] but concern about tardive dyskinesia has limited their usefulness.

The 3 patients described are all survivors of childhood abuse and neglect, which may predispose to complex forms of posttraumatic stress disorder[7] in addition to more typical forms of anxiety such as panic attacks or generalized anxiety disorder. None of these patients meet criteria for Axis II diagnoses, nor do any of them have prominent traits of personality disorders. All showed high levels of anxiety that included near-paranoid levels of concern that interactions with other people would lead to harm in some indefinable way. Given their lower risk of tardive dyskinesia[8] and extrapyramidal side effects, the atypical antipsychotics should be considered for use in nonpsychotic patients with depression and refractory anxiety, perhaps in particular those patients with complex posttraumatic stress complicating depression.

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