Receptor-Binding Profiles of Antipsychotics: Clinical Strategies When Switching Between Agents

Peter F. Buckley, M.D.

In spite of apparent improvements in the pharmacotherapy of schizophrenia, many patients still demonstrate an incomplete therapeutic response to antipsychotic medication and/or intolerable adverse effects, necessitating a change in their medication regimen. The switch from one antipsychotic to another, however, is not without challenges and can be complicated by withdrawal-emergent adverse effects that prompt the patient or the clinician to abort the switch. The extent to which these adverse events can be predicted by comparing the effects of the old and new antipsychotic medications on various receptor systems, including dopaminergic, muscarinic, and histaminergic receptors, is of considerable clinical and research interest. For example, patients receiving a sedating antipsychotic with high affinity for histamine H_1 receptors could experience rebound insomnia if switched to a less sedating agent with a low affinity for H_1 receptors. An understanding of the differential receptor-binding profiles of the various antipsychotics can help clinicians anticipate and manage potential clinical issues that may be encountered when switching antipsychotic therapy.

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Many patients do not experience full symptomatic relief from their antipsychotic therapy, and still more experience adverse effects that reduce their quality of life, erode their health, and increase medication noncompliance. In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, for example, 74% of patients discontinued their assigned medication within 18 months and switched to a new agent for phase 2.[1] Nearly a quarter of these patients, who received olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine, discontinued due to lack of efficacy, and approximately 15% discontinued because of intolerable adverse effects; the remainder of discontinuations were grouped under "patient decision." The CATIE study was naturalistic in design, and thus it seems likely that these numbers are representative of "real world" conditions. If so, the vast majority of patients will switch medications, likely several times, over the course of their treatment.

It is perhaps a cruel irony that the risk associated with switching antipsychotics emerged as clinicians gained experience with the second-generation antipsychotics that followed clozapine. Patients who were poor responders to clozapine and those who had found clozapine intolerable were offered the chance of switching to newer agents with more tolerable adverse effect profiles. In the absence of guidance and clinical experience, many clinicians (me included) instituted switching strategies that were short-lived and aimed to complete the transition quickly so as to limit the burden of 2 antipsychotics for the patient. The results of this approach were unforeseen and disconcerting; some patients relapsed, and some experienced distressing somatic (especially gastric) adverse effects and marked insomnia. Some patients and clinicians aborted the trial of the newer agent and returned to clozapine believing that they could at least get back to where they were before. Isolated reports of patients restarting clozapine, but experiencing a diminished response the second time around began to surface.[2] The cumulative effects of these adverse switching experiences prompted the National Institute of Mental Health to convene an expert panel conference to provide guidance to our field.[2] Various switching strategies were promulgated, none of which had been adequately tested in research. Published clinical switch studies are most often open-label and lack a control as comparator, offering little empirical research direction. The maxims of "switch slowly" and "cross-taper" emerged as psychopharmacologic "wisdom" reflecting appropriate conservatism and

From the Department of Psychiatry, Medical College of Georgia, Augusta.

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Corresponding author and reprints: Peter F. Buckley, M.D., Medical College of Georgia, Department of Psychiatry, 1515 Pope Ave., Augusta, GA 30912 (e-mail: pbuckley@mail.mcg.edu).

Table 1. Receptor Potencies of Selected Antipsychotic Agents[a]

Receptor	Aripiprazole*†	Olanzapine‡§‖	Risperidone§‖	Quetiapine§‖	Ziprasidonel¶	Clozapine§‖	Haloperidol§‖
D_1	410[b]	31	75	455	9.5	85	25
D_2	0.34[b]	11	3	160	4.8	125	1
D_3	0.8[b]	49	14	340	7.2	280	2.7
D_4	44[b]	27	7	1600	39	21	5
5-HT_{1A}	1.7[b]	> 1000	490	2450	3.4	770	7930
5-HT_{2A}	3.4[b]	4	0.6	220	0.4	12	78
5-HT_{2C}	15[b]	11	26	615	1.3	8	3085
α_1	57	19	2	7	10	7	46
H_1	61[b]	7	155	11	47	6	3630
M_1	> 10,000	1.9	> 5000	120	> 10,000	1.9	1475

[a]Reprinted with permission from Gardner et al.[4] Data are in K_i values (nM) determined by radioligands for binding to the indicated receptors and are presented in order of decreasing affinity for dopamine D_2L (predominant long form, based on gene splice variants) receptors. Original sources of the data are as follows: *Abilify [package insert]. Princeton, NJ: and Rockville, Md: Bristol-Myers Squibb and Otsuka America Pharmaceutical; 2005. †Lawler CP, et al. Neuropsychopharmacology 1999;20:612–627. ‡Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2005. §Bymaster FP, et al. Neuropsychopharmacology 1996;14:87–96. ‖Arnt J, Skarsfeldt T. Neuropsychopharmacology 1998;18:63–101. ¶Geodon [package insert]. New York, NY: Pfizer Inc; 2005.
[b]Data with cloned human receptors.

an appreciation of the inherent risks of switching medications (rather than the result of 1 or several pivotal studies). A further iteration of this psychopharmacologic philosophy is elaborated below, now fueled by a consideration of the receptor profile of each drug during the switching process.

The basic premise is that medication switches may go more smoothly and be associated with better outcomes if the switches occur slowly and with consideration of the receptor-binding profiles of the old and new medications, which directly mediate the differential risk for developing certain adverse events. Such differences in receptor-binding profiles can result in withdrawal-emergent adverse events that can sabotage attempts to improve patient therapy. Clinicians who are familiar with the activity of common antipsychotics in the dopaminergic, muscarinic, and histaminergic neurotransmitter systems can predict likely interactions between the old and new medications and subsequently prepare their patients for these transient effects, ideally taking steps to minimize them with slow switching and perhaps some judicious, but appropriate, use of adjunctive medications, thus improving their patients' chances of achieving the best possible treatment outcome.

Schizophrenia is thought to possess a neurochemical "signature" of low cortical dopamine and frontal lobe dysfunction, which is associated with negative symptoms, and an increase in subcortical dopamine activity, which is associated with positive symptoms.[3] First-generation antipsychotics are primarily dopamine antagonists, which lower the dopamine activity in the subcortical regions and reduce positive symptoms. In relative contrast, second-generation antipsychotics generally combine dopamine antagonism with activity in other receptor systems, such as the serotonin 5-HT_{2A}, muscarinic cholinergic, adrenergic, and H_1 histaminergic systems[4] (Table 1). It is thought that efficacy is mediated primarily by the dopaminergic and serotonergic, and possibly cholinergic, activity of an agent, whereas the action at other sites results in adverse effects. The following sections will elaborate on these themes.

DOPAMINERGIC CONSIDERATIONS

Parkinsonism, and possibly other extrapyramidal symptoms (EPS), are the result of dopamine antagonism in the forebrain basal ganglia. Elevated prolactin levels, another expression of dopaminergic blockade, are a result of the inhibition of D_2 receptors in the anterior-pituitary mammotropic cells.[4] For first-generation dopamine antagonist antipsychotics, there is a narrow dose range in which sufficient dopamine receptors are occupied to produce a clinical response (≥ 65% occupancy); higher occupancies are associated with dopamine-antagonism–related adverse events such as elevated prolactin (~ 72% occupancy) and EPS (> 78% occupancy).[5] Thus, among first-generation D_2 antagonists, D_2-receptor affinity and occupancy predict antipsychotic response, as well as EPS, akathisia, and prolactin elevation.[5] Unfortunately, wide interpersonal variation in the dose required for optimal receptor occupancy means that there is no single dose for all patients that will guarantee clinical response without adverse events.[5]

Second-generation antipsychotics vary widely in their affinity and activity at the D_2 receptor. The affinities at D_2 receptors for risperidone (3 nM), ziprasidone (4.8 nM), and olanzapine (11 nM) are more than 10-fold greater than those measured for clozapine (125 nM) and quetiapine (160 nM).[6,7] This difference in relative affinities for the D_2 receptor may explain the "glass ceiling" effect seen when dosing the low-affinity D_2-receptor antagonists, clozapine and quetiapine. Aripiprazole, on the other hand, represents the latest iteration of the dopamine hypothesis of antipsychotic efficacy. Aripiprazole has a greater affinity for D_2 than the rest of the second-generation antipsychotics (0.34 nM), but acts as a partial D_2 agonist, mean-

ing that the effects of its affinity are different from those of D_2 antagonists.[8] As a high-affinity partial D_2 agonist, aripiprazole displaces endogenous dopamine from D_2-receptor–binding sites.[4] However, unlike D_2 antagonists, aripiprazole partially stimulates the receptor, albeit to a lesser degree than would endogenous dopamine or a full dopamine agonist. As a result, aripiprazole acts as a dopamine stabilizer, increasing dopamine transmission in the frontal cortex, where it is too low, and attenuating dopamine transmission in the subcortical regions, where it is too high.[3]

The remainder of the second-generation antipsychotics are dopamine antagonists. Arranged in order of descending D_2 affinity (K_i), they rank as follows: risperidone (3.3 nM) > ziprasidone (4.8 nM) > olanzapine (11 nM) > clozapine (125 nM) > quetiapine (160 nM). Among the dopamine antagonist antipsychotics, this differential affinity does not translate into different efficacy—likely because these agents achieve the level of binding required for efficacy—but does result in different adverse event profiles, because only some of them achieve the higher levels of binding that result in dopaminergic adverse events.[4] EPS, which require very high levels of receptor occupancy, occur occasionally with risperidone, the highest-affinity dopamine antagonist second-generation antipsychotic, but only rarely with the other second-generation antipsychotics. A more common adverse event with the second-generation antipsychotics is elevated prolactin, which is reflected by the lower level of receptor occupancy required for this adverse effect. In a hospital census study, 91% of patients receiving risperidone experienced elevated prolactin levels, as opposed to 40% of patients receiving olanzapine, 22% of patients receiving quetiapine, and 11% of patients receiving clozapine.[9] In a separate study, 21.9% of female patients receiving ziprasidone experienced elevated prolactin levels,[10] whereas in a pooled analysis of short-term, placebo-controlled trials of aripiprazole, 1.8% of patients with previously normal prolactin levels experienced an increase in their prolactin to above the upper limit of normal.[11] In most patients, aripiprazole is associated with a decrease in prolactin within normal limits,[12] as would be expected based on its partial-agonist, dopamine-stabilizing activity.

The brain adapts to dopamine antagonists, which can be problematic when medication is discontinued. Prolonged treatment with D_2 antagonists (first- and second-generation antipsychotics) was found in an earlier imaging study to result in an approximately 34% increase in dopamine binding relative to normal controls, although there was considerable variability in patient responses, including some patients who experienced no increase in D_2 binding and some patients who experienced an increase in excess of 34%.[13] The patient with the greatest increase in D_2 binding relative to controls also experienced severe, persistent tardive dyskinesia upon discontinuing previous medication and beginning treatment with quetiapine.

Switch-emergent tardive dyskinesia has been reported as a dopaminergic-rebound event that occurs when a patient who has been maintained on an antipsychotic with a high D_2-binding potential and has experienced D_2 up-regulation is switched to an antipsychotic with low D_2-receptor occupancy; very transient D_2-receptor occupancy, as in the case of quetiapine; or partial D_2 agonism, as with aripiprazole. It is postulated that when supersensitive mesolimbic dopamine receptors encounter lower levels of D_2 antagonism, or outright D_2 agonism, EPS and tardive dyskinesia may appear. Dopamine supersensitivity in the mesolimbic pathway could produce a similar rebound effect perhaps resulting in switch-emergent dopamine psychosis,[14] which can be distinguished from true relapse by its rapid onset after medication discontinuation or taper. In practice, such distinctions may be less apparent and may be obfuscated by the clinical presentation.

Although too-rapid discontinuation of an antipsychotic with a high D_2 affinity may result in withdrawal-emergent adverse effects, patients should also be informed about anticipated, or at least potential, benefits of switching medications. These may include a decrease in prolactin levels; improvement in prolactin-related adverse effects such as galactorrhea, amenorrhea, and sexual dysfunction; and a decrease in EPS. Thus, there seems to be intuitive merit in considering the dopaminergic profiles of the old and new drugs and in plotting a slow, gradual switch that gives the brain time to adapt to changing levels of dopaminergic stimulation.

MUSCARINIC CONSIDERATIONS

The muscarinic receptor system is associated with cognition, memory, motor activity, and sleep, all of which are commonly disrupted in schizophrenia.[15] The anticholinergic activities of some second-generation antipsychotics are thought to contribute to the low incidence of EPS associated with these medications and, possibly, their antipsychotic activity; excessive cholinergic tone is thought to contribute to psychosis in susceptible patients.[15] Of the available second-generation antipsychotics, olanzapine (K_i 1.9 nM), clozapine (K_i 7.5 nM), and, to a lesser extent, quetiapine (K_i 120 nM) have the greatest affinity for the muscarinic acetylcholine receptors, whereas aripiprazole, risperidone, and ziprasidone have minimal affinity (K_i > 10,000 nM).[4]

There is the potential for patients who have been maintained on an anticholinergic antipsychotic to develop cholinergic supersensitivity and display symptoms such as nausea, vomiting, diaphoresis, and insomnia either when the anticholinergic medication is withdrawn or when they are being switched to a medication with less potent anticholinergic effects.[16] Slow tapering of an anti-

psychotic with anticholinergic properties may minimize the possibility of rebound in some patients being switched between second-generation antipsychotics. Adjunctive anticholinergic agents, such as benztropine mesylate, may also be helpful in managing this transition.[17] Whether these drugs should be continued, or added preemptively during a switch of antipsychotic medications, is not clear. Such strategies have not been comparatively evaluated yet.

HISTAMINERGIC CONSIDERATIONS

H_1 affinity and drug dose interact to produce sedation and weight gain.[18] Of the common second-generation antipsychotics, clozapine has the highest affinity (K_i) for H_1 (2.8 nM), followed by olanzapine (7.1 nM), quetiapine (11 nM), ziprasidone (46.8 nM), risperidone (58.8 nM), and aripiprazole (61 nM).[4] In general, antipsychotics with greater H_1 affinities will be associated with more sedation and weight gain, but even low-affinity medications will stimulate H_1 receptors if given in sufficient doses. Quetiapine, for example, has a much lower H_1 affinity than other second-generation antipsychotics, but because it is given in larger doses than other antipsychotics, it is associated with sedation. At commonly prescribed doses, olanzapine is associated with the greatest sedation of the commonly used second-generation antipsychotics (20%–40%), followed by ziprasidone (14%–24%), quetiapine (6%–11%), risperidone (3%–10%), and aripiprazole (3%–11%).[11,18,19]

Histaminergic activity also correlates with weight gain as well as the incidence of type 2 diabetes.[20,21] As would be expected from its affinity for the H_1 receptor, clozapine is associated with more weight gain than olanzapine, risperidone, or ziprasidone: 3.99 kg (8.78 lb), 3.51 kg (7.72 lb), 2.00 kg (4.4 lb), and 0.04 kg (0.88 lb), respectively, during a 10-week period.[22] Similarly, in the CATIE study, olanzapine was associated with the greatest weight gain, an average of 2 lb per month of treatment, followed by quetiapine (0.5 lb), risperidone (0.4 lb), and ziprasidone (–0.3 lb).[1] Aripiprazole was not included in phase 1 or 2 of CATIE, but data from a 26-week, head-to-head trial of aripiprazole and olanzapine showed that patients receiving olanzapine gained an average of 4.23 kg, whereas patients receiving aripiprazole lost an average of 1.37 kg ($p < .001$).[23] Additionally, olanzapine was associated with the greatest increase in blood glucose in CATIE: patients receiving olanzapine had an exposure-adjusted mean increase in glucose of 13.7 mg/dL, followed by quetiapine (7.5 mg/dL), risperidone (6.6 mg/dL), and ziprasidone (2.9 mg/dL).[1] Aripiprazole was not evaluated in CATIE, but has been shown to improve insulin resistance in patients previously taking second-generation antipsychotics associated with insulin resistance.[24]

Switching from a medication with a high H_1 affinity to one with a lower affinity offers the potential benefit of decreased sedation and an improvement in metabolic measures. On the other hand, this type of switch may be accompanied by rebound insomnia.[25] This can be distressing to the patient and may appear worrisome to both the patient and his or her family as a sign of impending relapse during the switch. It is important to alert the patient to the risk of insomnia during a switch. Rebound insomnia usually resolves with time, and this adverse effect can be minimized or avoided by changing medications slowly and using adjunctive benzodiazepines as needed during the switching period. However, whether the latter strategy is warranted and/or is associated with its own difficulties has not been appropriately studied as of yet.

CONCLUSION

The dopaminergic, muscarinic, and histaminergic tracts play key roles in both the adverse effects that necessitate many medication switches and the withdrawal-emergent adverse effects that can complicate these switches. Excessive D_2-receptor blockade can cause EPS and hyperprolactinemia. On the other hand, abrupt removal of that blockade opens sensitized receptors to excessive stimulation, which can result in emergent withdrawal EPS or perhaps even features of supersensitivity dopamine psychosis. Too-rapid removal of antipsychotics with high anticholinergic potency results in the severe flu-like symptoms of cholinergic rebound. Replacing a high H_1 affinity antipsychotic with a lower affinity one can alleviate sedation and metabolic effects, but this strategy can result in rebound insomnia. Switching medications is challenging. It is also important to appreciate that while this article presented receptor effects on a single system as if they occurred in isolation, the drugs we use are complex and thus there are likely to be multiple effects in action (and possibly in opposing directions) during a switch of medications. The science of switching is still a long way from "the clinical art" of switching antipsychotics. However, it does appear useful when switching medications to consider the receptor-binding profiles of the old and new medications. Such considerations may reveal the types of events likely to occur when switching, and thereupon allow the clinician to minimize the risk of these events by plotting a slow, gradual cross-titration and using appropriate adjunctive medications to manage the transition. Clearly, this is an area in need of research to refine practices and to evaluate the "neurochemical" propositions that are espoused in this article.

Drug names: aripiprazole (Abilify), benztropine mesylate (Cogentin and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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