The Clinical Implications of Antipsychotic Pharmacology

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Introduction

A general understanding of the pharmacology of antipsychotic medications is an important aspect of interpreting and translating clinical data into optimal clinical practice. With a growing number of pharmacologically distinct antipsychotic medications now available, treatment providers should be aware of clinically important pharmacokinetic and pharmacodynamic differences between antipsychotics that may influence medication selection, prescribing and monitoring.

Defining Drug Affinity, Potency and Receptor Interactions

There are a number of terms that are relevant to understanding the pharmacology of antipsychotic medications. For the purposes of this paper, a ligand is an antipsychotic that interacts with a neurotransmitter receptor binding site. This interaction results in a conformational change of the receptor that produces a physiological response. The interaction between an antipsychotic and a receptor is described, in part, by the drug's affinity for that receptor. If a drug has high binding affinity, there is greater intermolecular force between the drug and its receptor. This usually translates into a longer interaction between drug and receptor. This might also suggest a more pharmacologically active drug-receptor interaction, because a stronger and longer interaction between drug and receptor is more likely to lead to conformational change of the receptor and a physiological response.

Low affinity binding involves less intermolecular force between the drug and its receptor and usually a more transient or "loose" binding of drug to receptor. However, it is important to note that the length of time a drug is bound or the "tightness" of a drug binding to its receptor does not necessary correlate with affinity to the receptor. For example, aripiprazole has a very high affinity for the dopamine D_2 receptor, but its dissociation from the D_2 receptor is rapid (less than 1 minute), while haloperidol has comparable affinity for the D_2 receptor to aripiprazole but its dissociation from that receptor is amongst the slowest of the antipsychotics, at up to nearly 40 minutes.[1,2]

Binding affinity alone does not determine the overall potency of a drug. Potency is determined by binding affinity and the ligand efficacy, which is determined by the ligand's ability to produce a biological response and the magnitude of the response when it is bound to the receptor.

A drug that binds to a receptor, alters the function of the receptor, and triggers a physiological response is called an agonist. A higher-affinity drug requires lower concentrations to affect change in its receptor, while low-affinity drugs require higher concentrations to affect the same response. If a drug is only able to partially activate a receptor or is unable to fully affect a physiological response, the drug is referred to as a partial agonist. Receptor antagonists are not able to cause physiological response at a specific receptor and block binding by other ligands.

It has become convention to use inhibition constants (K_i) to compare relative receptor affinities between antipsychotics. The K_i value is the concentration of an antipsychotic (in a competition assay) required to occupy 50% of receptors under study (*e.g.,* D_2 receptors). The

higher the drug's affinity for the receptor, the lower the K_i. The K_i does not provide information about the drug's specific physiological impact at the receptor, but only the concentration of drug required to bind to half of the receptor binding sites. One drawback with comparing K_i values within a class of medication is that each agent may have a wide range of published values. In many cases, laboratories use different methodologies, different competitive ligands, and different sources of tissue that account for K_i variability. It is generally best to focus on relative receptor K_i differences (comparing one drug against another) rather than absolute numbers, which are highly variable.[3-6]

With a growing number of pharmacologically distinct antipsychotic medications now available, treatment providers should be aware of clinically important pharmacokinetic and pharmacodynamic differences between antipsychotics that may influence medication selection, prescribing and monitoring.

Using Antipsychotics in Clinical Practice

There are over a dozen antipsychotics available on the Canadian market. The majority are first-generation antipsychotics (FGAs), which have a primary mechanism of action of D_2 receptor antagonism. These agents have a spectrum of affinity for the D_2 receptor that ranges from low (*e.g.,* chlorpromazine) to high (*e.g.,* haloperidol). Generally, low-affinity FGAs are more sedating and have lower rates of extrapyramidal side effects than FGAs with high affinity for the D_2 receptor.

All but one of the newer antipsychotics available in Canada are called second-generation antipsychotics (SGAs) and antagonize both D_2 and $5HT_{2A}$ receptors. The SGAs have a lower affinity for the D_2 receptor than for the $5HT_{2A}$ receptor, and this dual antagonism is likely responsible for their efficacy and side-effect profiles differentiating FGAs from SGAs; particularly related to extrapyramidal side effects and negative symptoms.[7] Aripiprazole is the only partial D_2 agonist available on the Canadian market, and also acts as a $5HT_{1A}$ partial agonist and $5HT_{2A}$ antagonist. Aripiprazole is sometimes referred to as a third-generation antipsychotic (TGA) because of its unique D_2 partial agonism activity.[2,8,9]

The use of S/TGAs has broadened in recent years, as comfort using these agents has grown in a variety of clinical settings. S/TGAs are now commonly prescribed not just for schizophrenia and other psychotic disorders, but also for bipolar spectrum disorders, major depression, a range of anxiety disorders, autism, and for the management of disruptive behaviours. There is now a wide range of agents to choose from when confronted with a patient who might benefit from an antipsychotic. This article aims to address clinical challenges related to antipsychotic selection, appropriate starting dose and titration schedules, how to switch between S/TGAs, and treatment-emergent adverse effects most likely to interfere with treatment adherence.

As with all treatment strategies in mental health, prescribing antipsychotic medication must be individualized for each patient. What one patient might find helpful, another might find ineffective or intolerable. The heterogeneity of treatment response and adverse effects is due to many factors. We do not yet fully understand the root cause of psychiatric disorders, and as a result our treatment choices are often determined by symptom profile rather than biomarkers or genotype. The heterogeneity of psychiatric disorders means that every patient with bipolar I, as an example, will not respond the same way to a specific agent. Large population samples are rare in psychiatry and may provide clinicians with trends, but how each patient responds to a specific treatment is highly individual.[26]

TABLE 1.
Atypical Antipsychotic Indications in Canada and USA[10-25]

Antipsychotic	Indications by Country United States	Canada
Aripiprazole	• Schizophrenia in adults & adolescents • Bipolar I disorder: - acute manic and mixed episodes in adults & adolescents - maintenance for BPI • Adjunctive treatment for MDD • Irritability associated with autism in children • Injection used for acute treatment of agitation in schizophrenia and BPI	• Schizophrenia • Bipolar I disorder: acute manic and mixed episodes
Clozapine	• Treatment-resistant schizophrenia	• Treatment-resistant schizophrenia (only dispensed through the Clozaril Support and Assistance Network [CSAN])
Olanzapine	• Schizophrenia • Bipolar I disorder (acute and maintenance) • Depressive episodes associated with bipolar disorder • Treatment-resistant depression	• Schizophrenia • Bipolar I disorder (acute and maintenance)
Paliperidone	• Schizophrenia • Schizoaffective disorder	• Schizophrenia and related psychotic disorders
Quetiapine	• Schizophrenia • Bipolar I disorder (acute and maintenance) • Depressive episodes associated with bipolar I disorder • Major depressive disorder (XR only)	• Schizophrenia • Bipolar disorders (acute) • Depressive episodes associated with bipolar disorders (acute) • Major depressive disorder (XR only)
Risperidone	• Schizophrenia • Bipolar I disorder • Irritability associated with autism in children	• Schizophrenia • Bipolar I disorder
Ziprasidone	• Schizophrenia in adults • Bipolar I disorder (acute and maintenance)	• Schizophrenia • Bipolar I disorder (acute)

Treatment adherence is also highly variable, and reasons for lack of adherence are as varied as our patients. Furthermore, a clinician's own comfort and knowledge of an antipsychotic medication in terms of dosing, titration, appropriate switching strategies, or optimal augmentation strategies might have a significant impact on

TABLE 2.
Side Effect and Metabolic Profile of Atypical Antipsychotics[38-43]

Antipsychotic	EPS	QTc Prolongation	Sedation	Sexual Dysfunction	Hyper-lipidemia	Weight Gain	Diabetes Risk	Dyslipidemia
Aripiprazole	Low	Low	Low	Low	Low	Low	Low	Low
Olanzapine	Low	Low	Moderate	Low	High	High	High	High
Quetiapine	Low	Low	High	Low	Moderate	Moderate	Low	High
Risperidone	Moderate	Low	Low	Moderate	High	Moderate	Moderate	Moderate
Ziprasidone	Low	Moderate	Low	Low	Low	Low	Low	Low

Low risk Moderate risk High risk

treatment effectiveness and outcome. Finally, a clinician's ability to create a therapeutic alliance that engenders trust and disclosure and the ability of each patient to work effectively with their clinician varies greatly.

Selecting an Antipsychotic Medication

Determining which agent to choose first for a particular patient is dependent on several factors. Paramount are the clinician's comfort with the agent with regard to safety and efficacy, the product indications and common off-label uses, the clinician's understanding of the common attributes of the agent (*e.g.,* sedation, activation), and the patient's symptom profile. While their widespread use in Canada suggests that most clinician's agree the S/TGAs are preferable to FGAs, the debate continues as to whether these newer agents are cost-effective and are better choices for all symptom domains.

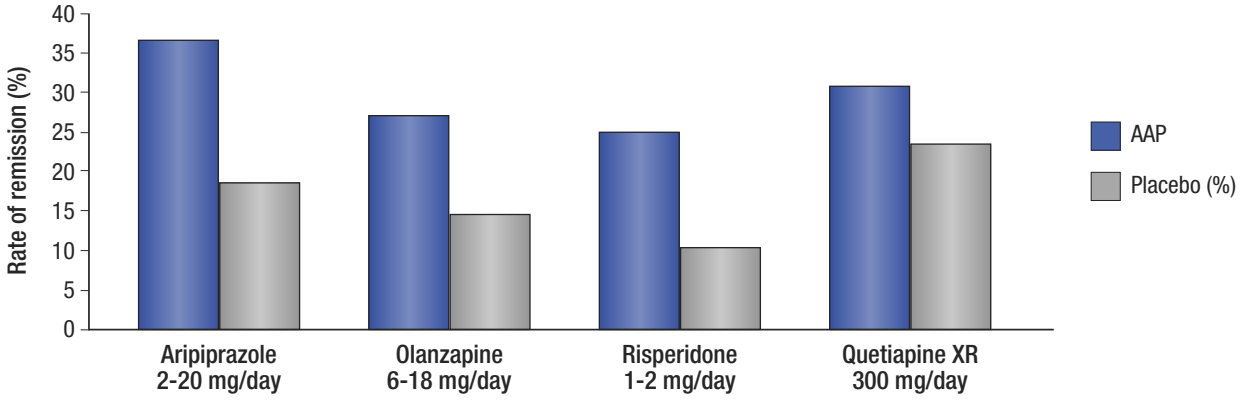
As with all treatment strategies in mental health, prescribing antipsychotic medication must be individualized for each patient.

S/TGAs are often preferred over FGAs because they are generally considered to have a lower risk of extrapyramidal side effects and TD. There are data suggesting that S/TGAs improve negative symptoms (*e.g.,* amotivation, apathy, avolition), have lower rates of hyperprolactinemia, except for risperidone and paliperidone, and are associated with improved quality of life (QoL).[27-29] Numerous double-blind studies comparing S/TGAs with FGAs have found better efficacy and tolerability for S/TGAs, although diagnosis does impact these factors. However, issues that include weight gain and other metabolic effects attributed to some of the SGAs have fueled healthy debate about the risk:benefit ratio and cost effectiveness of the SGAs, resulting in numerous clinical trials. Some authors have concluded that SGAs do not markedly differ from FGAs regarding compliance, QoL, and effectiveness. However, other studies that collected long-term data of antipsychotic treatment indicate that patients treated with SGAs had a greater chance of reaching remission than those receiving FGAs. Moreover, some of these studies have also concluded that patients' subjective well-being increased significantly more with SGAs compared with FGAs.[30-35]

The two most relevant advantages of SGAs versus FGAs are the better subjective effects and a reduced

FIGURE 1.

Rates of Remission of Adjunctive Atypical Antipsychotic (AAP) Therapy in Major Depressive Disorder[47,48,50,51]



Remission rates should not be compared between the above listed antipsychotics as these data do not reflect head-to-head studies.
No placebo controls available for ziprasidone.

risk of tardive dyskinesia. In a survey by Karow et al, 61 "experts by experience" (*i.e.,* schizophrenia patients who had been treated with SGAs for two years and before or afterwards with FGAs for one year) described marked differences, not in efficacy on positive symptoms, but on negative and affective symptoms, and also better tolerability regarding motor and sexual adverse effects.[36]

Excessive sedation and metabolic syndrome risk remain key adverse effects to consider when making an initial treatment choice. The most sedating agents (quetiapine, quetiapine XR, olanzapine and risperidone) might be chosen first line for patients with significant insomnia or agitation. However, benzodiazepines might be used short-term for patients where urgent sedation is desired, if metabolic risk factors are considerable. More activating agents (aripiprazole, ziprasidone, and paliperidone) might be preferred for slowed-down, fatigued patients. For patients with the greatest aversion to weight gain and those who are already overweight or have risk factors for metabolic syndrome, clinicians should consider aripiprazole, ziprasidone, and paliperidone because of their lower risk of metabolic adverse effects.[37-43]

S/TGA Indications and Common Uses

All S/TGAs in Canada are indicated for the treatment of schizophrenia and related psychotic disorders, as well as Bipolar I mania.[40,44-46] However, there are certain agents that have demonstrated efficacy for other psychiatric disorders and others that are widely used outside their product indications. Quetiapine XR monotherapy has the indication for bipolar depression and major depressive disorder (MDD). Currently, quetiapine XR is the only antipsychotic with the MDD indication in Canada. Olanzapine has also displayed efficacy for bipolar depression when used in combination with an SSRI. Aripiprazole monotherapy does not have the indication for MDD;

The two most relevant advantages of SGAs versus FGAs are the better subjective effects and a reduced risk of tardive dyskinesia.

TABLE 3.
Serotonin and Dopamine Receptor Affinities of Atypical Antipsychotics[8]

Antipsychotic	5-HT_{2A}	5-HT_{2C}	5-HT_{1A}	D_2/D_3
Aripiprazole	+++	+++	+++	++++
Olanzapine	+++	+++	-	+++
Quetiapine XR	++	+	-	++
Risperidone	++++	+++	-	+++
Ziprasidone	++++	+++	+++	+++

however the 2009 CANMAT guidelines for MDD included aripiprazole among first-line add-on agents for the treatment of MDD, along with olanzapine and risperidone. There are many open-label and several randomized controlled trials showing the benefits of using S/TGAs in combination with antidepressants for a variety for anxiety disorders, including post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and generalized anxiety disorder (GAD).[47-49]

There are several reasons why some S/TGAs may be effective for treating depression, while others are not. Excess D_2 receptor antagonism can interfere with antidepressant effects, so agents with greater D_2 antagonism may in fact confer a depressogenic effect. It has been hypothesized that antipsychotics with a stronger D_2 blockade may be more likely to induce depression or counteract the antidepressant effects that a drug might have through another mechanism.[52] A review of relative D_2 receptor affinities shows that quetiapine has a very low D_2 antagonism compared to olanzapine and even more so, risperidone. Haloperidol, with extremely high D_2 receptor antagonism, may induce depressive symptoms.[10-25,53,54]

There are many open-label and several randomized controlled trials showing the benefits of using S/TGAs in combination with antidepressants for a variety of anxiety disorders.

As noted above, atypical antipsychotics interact with other receptor types that might confer an antidepressant effect. One antidepressant mechanism is serotonin $(5HT)_{2A}$ receptor antagonism. All antidepressants that effect serotonin, including ECT, down-regulate $5HT_{2A}$ receptors. As well, nearly all S/TGAs downregulate $5HT_{2A}$ receptors, correlating with an antidepressant effect. Antagonism of the $5HT_{2A}$ receptor also causes an increase in both dopamine (DA) and norepinephrine (NE), which counteracts, in certain brain areas, D_2 antagonism.

Many antidepressants also exert their pharmacological effects by antagonizing presynaptic neurotransmitter transporters for NE, 5HT and DA. A few antidepressants also act as $5HT_{1A}$ partial agonists which confers antidepressant as well as anxiolytic properties. These pharmacological mechanisms are also shared by some antipsychotics as follows: 1) ziprasidone inhibits NE and 5HT transporters and is also a $5HT_{1A}$ partial agonist; 2) quetiapine's active metabolite, norquetiapine, antagonises NE transporters; and 3) aripiprazole is a $5HT_{1A}$ partial antagonist.[52]

While some atypical antipsychotics are activating (*e.g.,* aripiprazole, paliperidone) and others are more sedating (*e.g.,* quetiapine, olanzapine), this does not imply that a particular agent should be avoided in anxious, agitated, or psychomotor-retarded patients. Successful treatment of

TABLE 4.
Initial Dose and Titration of Atypical Antipsychotics in Bipolar Disorders*[11,15-25]

	Aripiprazole	Olanzapine	Quetiapine XR	Risperidone	Ziprasidone
$T_{1/2}$	75 hours	21-54 hours	6-7 hours	17-23 hours	6-10 hours
Bipolar Depression	N/I	** 5 mg in combination with fluoxetine	50 mg (up to 300 mg/day)	N/I	N/I
Acute Mania	Mania: - Starting dose 15 mg/day (up to a maximum of 30 mg/day)	For mixed episodes: • 10-15 mg QD • 10 mg QD with Li/Va - Agitation associated with bipolar mania: 10 mg IM	300 mg (up to 800 mg/day)	2-3 mg/day (up to 6 mg/day)	Mania: - Start at 40 mg BID with food - Titrate to 60-80 mg BID - Efficacy dose range 40-80 mg/day BID
Maintenance	Same dose used to stabilize patient during acute treatment	5-20 mg/day	Effective dose range: - 400-800 mg/day for mania - 300 mg/day target for BPD (up to 600 mg)	No long-term data (> 3 weeks) to guide clinicians	As an adjunct to Li/Va, same dose used to stabilize patient during acute treatment**

*based on product monographs
**based on U.S. product monograph

the underlying disorder may indirectly lead to resolution of these symptoms. Not unlike antidepressants, some of the same mechanisms that provide an antidepressant effect also are anxiolytic. Agitation is a common presentation associated with bipolar mania and acute schizophrenia, and all S/TGAs are indicated for those disorders. If a more activating agent is desired, and there is concern about increasing agitation or anxiety transiently, the use of an intermediate half-life benzodiazepine, such as lorazepam or clonazepam, is recommended.[55]

Initial Dose and Titration

The initial dose of an antipsychotic depends primarily on the psychiatric diagnosis and the acuity of the illness. However, previous treatment response, the presence of other medications, and personal history of medication tolerability should also be considered. Acute mania or severe psychotic symptoms usually require higher initial doses and more aggressive titration, if titration is necessary. However, starting at the higher end of the dose range leads to intolerability for some patients and increases the likelihood of non-adherence. This may result in a lost opportunity, which might have been avoided by taking some extra time to titrate the dose. The use of intermediate half-life benzodiazepines (*e.g.,* lorazepam, clonazepam), to manage initial agitation and anxiety, may provide the clinician needed time to carefully and appropriately titrate the antipsychotic, thereby improving tolerability and adherence.

Dose ranges provided by product monographs may exceed or be lower than doses commonly prescribed in clin-

· TABLE 5.
Initial and Maintenance Doses of Atypical Antipsychotics in MDD[16,17,23,24]

	Aripiprazole* (adjunctive therapy)	Quetiapine XR (monotherapy)
Starting dose	2-5 mg/day (adjunct treatment)	50 mg/day on day 1, up to 150 mg on day 3
Maintenance	- up to15 mg/day maximum dose for patients on paroxetine CR or fluoxetine - 20 mg/day for all other patients	50-300 mg/day (doses > 300 mg/day have not been evaluated)

*U.S. Abilify product monograph

ical practice. These drug doses are established using data from clinical trials. However, there are limitations associated with these doses because patients in trials are often not reflective of "real-world" patients seen in the community. For instance, clinical trials often exclude patients with comorbidities including substance abuse. The resultant demographic profile certainly does not reflect the majority of psychiatric patients. While "off-label" drug use, including dosing outside the product monograph recommendations and using a drug for a purpose other than its indication, is commonplace in psychiatry, the risks and benefits must be discussed with patients and documented in their chart.

Dose ranges provided by product monographs may exceed or be lower than doses commonly prescribed in clinical practice.

Generally speaking, lower doses of atypical antipsychotics are required when they are prescribed for mood or anxiety disorders. While quetiapine XR is currently the only antipsychotic that has the official indication for MDD as monotherapy, aripiprazole, olanzapine, and risperidone are also commonly used as adjunctive therapy to an antidepressant for the treatment of MDD. The U.S. product monograph suggests aripiprazole starting doses of 2-5 mg and maintenance doses ranging from 15-20 mg when used in concert with an antidepressant. While doses of 15 mg or more are sometimes required, the majority of patients are adequately treated in the range of 2-10 mg. Olanzapine has been shown to be effective for treatment-resistant depression when combined with fluoxetine. The dose range of olanzapine is usually 2-10 mg. Quetiapine doses for non-psychotic disorders like depression are often lower (100-150 mg) but some patients may require doses of 300 mg or more. Risperdone is usually beneficial in combination with an antidepressant at doses less than 1 mg. Doses in the 1.5 mg range may be required for some patients although doses above 1 mg sometimes results in a depressogenic effect. Ziprasidone, risperidone and aripiprazole are not indicated for bipolar depression but they are commonly used in this disorder, in combination with antidepressants or mood stabilizers. The doses required are similar to doses used for MDD or bipolar maintenance.

The titration schedule for antipsychotics depends on variables such as the half-life of the agent, drug tolerability, severity of illness and whether the patient is hospitalized. Aripiprazole has the longest half-life when compared to the SGAs, at 75 hours (and the active metabolite has a $T_{1/2}$ of 96 hours). This means to reach steady state for a given dose requires 2 weeks (4.5 half-lives to reach steady state x 75 hours = 337.5 hours or 14 days). Aripiprazole is the newest antipsychotic on the Canadian market, and many clinicians do not have experience with an oral antipsychotic agent with such a long half-life. As a consequence, some clinicians

TABLE 6.
Antipsychotic Affinity for Dopamine (D_2), α-adrenergic (α_1), Muscarinic (M_1), and Histaminic (H_1) Receptors[8,59-61]

Antipsychotic	D_2	α_1	M_1	H_1
*Aripiprazole	++++	+	-	+
Olanzapine	+++	++	+++	+++
Quetiapine XR	++	+++	++	++
Risperidone	+++	+++	-	-
Ziprasidone	+++	++	-	-

*Aripiprazole is a partial agonist (see explanation earlier in this article).

have titrated the dose of aripiprazole too quickly, resulting in higher than required doses and unnecessary side effects. Patients in less acute situations should start at doses of 2-5 mg and dose increases should occur no more rapidly than every two weeks. It should be noted that the approved product monograph suggests dose increases no more frequently than weekly. Antipsychotics with much shorter half-lives such as quetiapine (6-7 hours) or ziprasidone (6-10 hours) will reach steady state much more rapidly (4.5 half-lives to reach steady state x 6-10 hours = 27-45 hours or 1-2 days). This allows for more rapid titration. In several trials, quetiapine was titrated daily by 50-100 mg to therapeutic dose with good tolerability.[16,18,20,23,25]

Some clinicians express concern that an antipsychotic with a longer half-life might not be as effective initially. Half-life does not correlate with efficacy and onset of clinical benefit is not necessarily delayed. The drug is still active, and the therapeutic dose might be at the lower end of the dose range. A benefit of longer half-life agents is that missed doses are often not felt as acutely and are less likely to result in illness destabilization. Patients taking shorter half-life agents might experience worsening symptoms after missing one or two doses.

The initiation of ziprasidone holds some challenges; however, awareness of these challenges should increase its clinical effectiveness. Ziprasidone tends to be activating, particularly at lower doses, and this activation might feel like agitation for some patients upon initiation of treatment. This can be overcome by initiating ziprasidone at a higher dose. While most clinicians take a "start low, go slow" approach to most psychotropic agents, ziprasidone should be initiated at 60-80 mg/day, despite the availability of 40 mg capsules that some clinicians have divided to start at a cautious 20 mg/day. Doses lower than 60 mg/day are too activating or agitating for many patients, resulting in non-adherence. Another challenge with ziprasidone is the recommendation that the drug be taken with food in order to promote full absorption. This is particularly difficult for very ill patients that have a reduced appetite or those who cannot afford to eat regular meals. The adequate amount of food to assure full absorption of a dose of ziprasidone is 500 Kcal, which is considered a medium-calorie meal, and is not dependent on fat content. As examples, a 500 Kcal breakfast would consist of 1 cup of cereal, 1 piece of toast, an apple and a glass of milk. Finally, while ziprasidone is generally recommended to be dosed twice daily, once-daily dosing is common and effective in clinical practice, and increases the likelihood patients will take it with food, improving adherence.[25,39,41,56]

Quetiapine, due to a short half-life, reaches steady state rapidly. A rapid titration is possible, and sometimes patients experience less sedation at higher doses (above 150 mg). The potential mechanism for this effect is related to increasing NE due to blockade of NET. Quetiapine target doses are lower for mood and anxiety disorders (50-300 mg) than for bipolar disorder and psychosis (300-800 mg).

Paliperidone is available in 3, 6, and 9 mg tablets that may not be split or chewed. Because 3 mg is approximately equivalent to 1 mg risperidone, some clinicians find that dose too high for mood, anxiety, or elderly agitated patients, who commonly require 0.25-0.75 mg risperidone.[16,21,39]

Switching S/TGAs

Switching antipsychotics is a common treatment challenge for most clinicians. Clinicians must consider why the initial drug needs to be switched (*e.g.,* inefficacy, tolerability, cost), the severity or acuity of illness, the presence of comorbid conditions, other medications the patient is prescribed, and the pharmacokinetics and pharmacodynamics of both agents. Pharmacodynamics is often described as what a drug does to the body, whereas pharmacokinetics describes what the body does to a drug. Receptor profiles and affinities, including whether a drug is a receptor agonist, antagonist, or partial agonist, determine drug side effects, titration schedules, switch-emergent adverse effects, and the efficacy of combination therapies. When switching between antipsychotics, particular consideration must be given to the binding affinity differences between agents for the D_2, alpha adrenergic ($\alpha 1$), muscarinic (M_1), and histaminic (H_1) receptors. Moving from a high-affinity agent to a low-affinity agent may result in the emergence of adverse effects that might impact adherence.[8,57,58]

While "off-label" drug use, including dosing outside the product monograph recommendations and using a drug for a purpose other than its indication, is commonplace in psychiatry, the risks and benefits must be discussed with patients and documented in their charts.

Switching from a relatively lower-affinity D_2 receptor antagonist to a higher-affinity D_2 antagonist (*e.g.,* olanzapine to risperidone) may result in a D_2 receptor blockade-related dyskinesia. This may present as dyskinesia, Parkinsonism, akathisia, or acute dystonia. The onset is dependent on the rapidity of the switch and the relative affinity differences between the two agents. Sometimes the dyskinesia symptoms may occur within days of switch initiation. Management of this situation might require: 1) lowering the dose of the higher-affinity agent; 2) slowing the titration of the higher-affinity agent; 3) slowing the cross over (lower the dose of the lower-affinity agent more slowly); or 4) for akathisia, adding a beta blocker (10-40 mg tid) or a benzodiazepine (*e.g.,* lorazepam 1.5-3 mg/day in divided dose) during the cross over.[62,63]

In contrast, moving from a relatively high-affinity D_2 receptor antagonist to a lower-affinity agent might result in rebound or withdrawal dyskinesia, akathisia, or dystonia. Typical symptoms of akathisia may be indistinguishable from agitation or anxiety and occur within the first few days of switch initiation. Akathisia may be distinguished from agitation by an intense urge for movement, particularly in the legs, and symptom worsening that occurs as the dose is increased. Agitation generally improves as the dose of antipsychotic is increased. The addition of a beta blocker or a benzodiazepine might be helpful for akathisia-like symptoms. Breakthrough psychosis is also possible when switching from a relatively high-affinity D_2 receptor antagonist to a lower-affinity antagonist. As noted previously, problems related to D_2 receptor supersensitivity may be encountered when switching a patient from a high-affinity D_2 antagonist to aripiprazole, a D_2 receptor partial agonist. In this case, transient choreoathetoid movements or withdrawal dyskinesia, that is indistinguishable from TD, may occur within days.[64-66]

Switching a patient from a high-potency antipsychotic (*e.g.,* haloperidol or risperidone) to aripiprazole may result in the rapid appearance of withdrawal dyskinesias.

Unfortunately, many clinicians misinterpret this adverse event as the emergence of TD. Although the exact mechanism of this withdrawal dyskinesia is not fully understood, the following postulated pharmacological mechanism may offer a plausible explanation of this phenomenon: 1) discontinuing or reducing the dose of a high-potency antipsychotic exposes supersensitive D_2 receptors which, when agonized by endogenous dopamine, can lead to withdrawal dyskinesias independent of aripiprazole;[67,68] 2) as a partial D_2 agonist with approximately 30% intrinsic activity, aripiprazole will agonize some of these supersensitive D_2 receptors, thereby increasing the risk for developing withdrawal dyskinesias; and 3) aripiprazole's ability to increase dopamine release in the striatum (indirectly by its capacity to antagonize $5HT_{2A}$ receptors) increases the opportunity for dopamine to interact with the supersensitive D_2 receptors, thereby contributing to the withdrawal dyskinesia. Thus, any combination of these pharmacological mechanisms working in unison may explain the rapid emergence of withdrawal dyskinesias seen in patients being switched to aripiprazole.[69,70]

Choosing the correct method of switching between antipsychotics varies from patient to patient, but in many situations, a plateau cross-titration technique is appropriate. This involves starting the new agent while keeping the old agent at the current therapeutic dose. Once the new agent is titrated to what is expected to be a therapeutic dose, a slow taper of the old agent may commence. If symptoms of illness emerge, the tapering of the old agent is halted and the new agent is further increased. Once symptoms are stabilized, the tapering of the old agent may start again. Adverse effects related to starting one and stopping another agent are managed as they emerge. For instance, if agitation or insomnia occurs when switching from a more sedating to a less sedating antipsychotic, the short-term addition of a benzodiazepine might manage the problem quickly and allow the switch to continue. The only time when reduction of the old agent might be considered as the new agent is initiated is when switching from one highly sedating agent to another. For example, switching from olanzapine to quetiapine might require a simultaneous reduction in olanzapine along with the addition of quetiapine for sedation to be tolerable.

The time required to effectively execute a switch is dependent on the half-life of both agents and the patient's ability to tolerate withdrawal adverse effects. Switches between relatively short half-life agents may occur over a few weeks, while 6 or 8 weeks might be required when switching to an agent with a longer half-life like aripiprazole.[67,68,71] Dx

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References:

1. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry 2001; 158(3):360-9.
2. Mailman RB, Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des 2010; 16(5):488-501.
3. Grunder G, Carlsson A, Wong DF. Mechanism of new antipsychotic medications: occupancy is not just antagonism. Arch Gen Psychiatry 2003; 60(10):974-7.
4. Hoyer D, Boddeke HW. Partial agonists, full agonists, antagonists: dilemmas of definition. Trends Pharmacol Sci 1993; 14(7):270-5.
5. Inoue A, Nakata Y. Strategy for modulation of central dopamine transmission based on the partial agonist concept in schizophrenia therapy. Jpn J Pharmacol 2001; 86(4):376-80.
6. Tamminga CA. Partial dopamine agonists in the treatment of psychosis. J Neural Transm 2002; 109(3):411-20.
7. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry 2002; 47(1):27-38.
8. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry 2005; 10(1):79-104.
9. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28(8):1400-11.
10. INVEGA [package insert]. Janssen Inc., Toronto, 2010.
11. Risperdal [USA package insert]. Janssen Ortho LLC, Gurabo, 2010.
12. INVEGA [USA package insert]. Janssen Ortho LLC, Gurabo, 2010.
13. Clozaril [package insert]. Novartis Pharmaceuticals Canada Inc., Dorval, 2010.
14. Clozaril [USA package insert]. Novartis Pharmaceuticals Corporation, East Hanover, 2010.
15. SEROQUEL [USA package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, 2011.
16. SEROQUEL XR [package insert]. AstraZeneca Canada Inc., Mississauga, 2010.
17. SEROQUEL XR [USA package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, 2010.
18. Zyprexa [package insert]. Eli Lilly Canada Inc., Toronto, 2010.
19. Zyprexa [USA package insert]. Eli Lilly & Co, Indianapolis, 2010.
20. Zeldox [package insert]. Pfizer Canada Inc., Kirkland, 2010.
21. SEROQUEL [package insert]. AstraZeneca Canada Inc., Mississauga, 2010.
22. Geodon [package insert]. Pfizer, New York, 2010.
23. Abilify [package insert]. Bristol-Myers Squibb Canada, Montreal, 2010.
24. Abilify [USA package insert]. Bristol-Myers Squibb Company, Princeton, 2009.
25. Risperdal [package insert]. Janssen-Ortho Inc., Toronto, 2008.
26. Leboyer M, Kupfer DJ. Bipolar disorder: new perspectives in health care and prevention. J Clin Psychiatry 2010; 71(12):1689-95.

27. Wehmeier PM, Kluge M, Schneider E, Schacht A, Wagner T, Schreiber W. Quality of life and subjective well-being during treatment with antipsychotics in out-patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31(3):703-12.
28. de Millas W, Lambert M, Naber D. The impact of subjective well-being under neuroleptic treatment on compliance and remission. Dialogues Clin Neurosci 2006; 8(1):131-6.
29. Thase ME, Denko T. Pharmacotherapy of mood disorders. Annu Rev Clin Psychol 2008; 4:53-91.
30. Tamayo JM, Zarate CA, Jr., Vieta E, Vazquez G, Tohen M. Level of response and safety of pharmacological monotherapy in the treatment of acute bipolar I disorder phases: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2010; 13(6):813-32.
31. Marder SR, Essock SM, Miller AL, et al. The Mount Sinai conference on the pharmacotherapy of schizophrenia. Schizophr Bull 2002; 28(1):5-16.
32. Buckley PF. Update on the treatment and management of schizophrenia and bipolar disorder. CNS Spectr 2008; 13(2 Suppl 1):1-10; quiz 11-12.
33. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disord 2010; 12(2):116-41.
34. Correll CU, Hauser M, Auther AM, Cornblatt BA. Research in people with psychosis risk syndrome: a review of the current evidence and future directions. J Child Psychol Psychiatry 2010; 51(4):390-431.
35. Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs 2011; 71(1):43-64.
36. Karow A, Schnedler D, Naber D. What would the patient choose? Subjective comparison of atypical and typical neuroleptics. Pharmacopsychiatry 2006; 39(2):47-51.
37. Stahl SM. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* Second edition. Cambridge University Press, New York, 2000.
38. Miller DS, Yatham LN, Lam RW. Comparative efficacy of typical and atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of acute mania. J Clin Psychiatry 2001; 62(12):975-80.
39. Olfson M, Marcus SC, Corey-Lisle P, Tuomari AV, Hines P, L'Italien GJ. Hyperlipidemia following treatment with antipsychotic medications. Am J Psychiatry 2006; 163(10):1821-5.
40. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009; 11(3):225-55.
41. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacol 2004; 24(1):62-9.
42. Keck PE, Jr., Calabrese JR, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 2006; 67(4):626-37.
43. Kim B, Kim SJ, Son JI, Joo YH. Weight change in the acute treatment of bipolar I disorder: a naturalistic observational study of psychiatric inpatients. J Affect Disord 2008; 105(1-3):45-52.
44. Fountoulakis KN, Vieta E, Siamouli M, et al. Treatment of bipolar disorder: a complex treatment for a multi-faceted disorder. Ann Gen Psychiatry 2007; 6:27.
45. Winans E. Aripiprazole. Am J Health Syst Pharm 2003; 60(23):2437-45.
46. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord 2006; 8(6):721-39.
47. Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry 2009; 70(4):540-9.
48. Mahmoud RA, Pandina GJ, Turkoz I, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med 2007; 147(9):593-602.
49. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008; 28(2):156-65.
50. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr 2009; 14(4):197-206.
51. Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry 2007; 68(2):224-36.
52. Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. Biol Psychiatry 2001; 50(11):873-83.
53. Bishara D, Taylor D. Upcoming agents for the treatment of schizophrenia: mechanism of action, efficacy and tolerability. Drugs 2008; 68(16):2269-92.
54. Haloperidol. Available at: *www.drugs.com/mmx/haloperidol.html*. Accessed March 2011.
55. Zeller SL, Rhoades RW. Systematic reviews of assessment measures and pharmacologic treatments for agitation. Clin Ther 2010; 32(3):403-25.
56. Kutcher S, Brooks SJ, Gardner DM, et al. Expert Canadian consensus suggestions on the rational, clinical use of ziprasidone in the treatment of schizophrenia and related psychotic disorders. Neuropsychiatr Dis Treat 2005; 1(2):89-108.
57. Jibson MD, Tandon R. New atypical antipsychotic medications. J Psychiatr Res 1998; 32(3-4):215-28.
58. Stahl S. *Stahl's Illustrated Antipsychotics.* Cambridge University Press, New York, 2009.
59. Wood MD, Scott C, Clarke K, et al. Pharmacological profile of antipsychotics at monoamine receptors: atypicality beyond 5-HT2A receptor blockade. CNS Neurol Disord Drug Targets 2006; 5(4):445-52.
60. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry 2008; 13(1):27-35.
61. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov 2004; 3(4):353-9.
62. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 2000; 22(1):73-81.
63. Kane JM, Correll CU, Goff DC, et al. A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. J Clin Psychiatry 2009; 70(10):1348-57.
64. Day RK. Psychomotor agitation: poorly defined and badly measured. J Affect Disord 1999; 55(2-3):89-98.
65. Hirose S. The causes of underdiagnosing akathisia. Schizophr Bull 2003; 29(3):547-58.
66. American Psychiatric Association. *Treatment of Patients With Schizophrenia.* Second edition. Available at: *www.psychiatryonline.com/pracGuide/pracGuideChapToc_6.aspx*. Accessed March 2011.
67. Lambert TJ. Switching antipsychotic therapy: what to expect and clinical strategies for improving therapeutic outcomes. J Clin Psychiatry 2007; 68 (Suppl 6):10-13.
68. Liauw SS, McIntyre RS. Atypical antipsychotic tolerability and switching strategies in bipolar disorder. Expert Opin Pharmacother 2010; 11(17):2827-37.
69. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003; 61(2-3):123-36.
70. Urbano M, Spiegel D, Rai A. Atypical antipsychotic withdrawal dyskinesia in 4 patients with mood disorders. J Clin Psychopharmacol 2007; 27(6):705-7.
71. McDonagh M, Peterson K, Carson S, Fu R, Thakurta S. *Drug Class Review: Atypical Antipsychotic Drugs: Final Update 3 Report.* Oregon Health & Science University, Portland, 2010.