

SWITCHING AND COMBINING ANTIPSYCHOTICS

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Introduction

Pharmacologic knowledge can inform clinical decision-making, particularly the dosing and switching decisions made with antipsychotics. Of relevance are the pharmacokinetic (what does the body do to the drug) and the pharmacodynamic (what does the drug do to the body) properties of antipsychotics.

Real-Life Antipsychotic Dosing

The goal of antipsychotic dosing is to achieve sufficient dopamine blockade in areas where dopamine excess can lead to psychosis, mania, or aggression. Using positron emission topography, one investigation showed that response rates were considerably higher in patients who achieved >65% striatal dopamine blockade.[1] Conversely, striatal dopamine blockade >80% predicted the emergence of extrapyramidal symptoms (EPS) or akathisia.

There is, however, considerable intra-individual variability in achieving the desired 60% to 80% striatal dopamine blockade.[2] Such variability is likely due to inter-individual differences in the absorption, distribution, metabolism and elimination of medications. At the same time, antipsychotics themselves differ in their general pharmacokinetic profiles. For example, ziprasidone absorption is ~50% less when ingested on an empty stomach than when taken with a meal; the degree of absorption depends on the caloric content, while the fat content is not relevant.[3]

The bioavailability of individual antipsychotics is also affected by the liver enzymes principally related to the metabolism of each particular medication. The principal enzymes involved in metabolism of antipsychotics are cytochrome P450 3A6, 2A4, 2D6, and 1A2 (Slide 1).[4] Aripiprazole and risperidone are chiefly metabolized by 2D6, and quetiapine by 3A4. The 2D6 system is very much affected by polymorphisms, and has less capacity than 3A4. Therefore, medications that are chiefly metabolized by 2D6 may have greater variations. Clozapine and olanzapine are metabolized by 1A2. Smoking can accelerate 1A2, and smokers may require higher dosages, depending on changes in smoking patterns. Also, taking several medications that are metabolized by the same CYP 450 enzymes can slow down the metabolism of these medications.[5] Paliperidone and ziprasidone are least metabolized by CYP 450 enzymes, leading to the lowest metabolic drug-drug interactions.

SLIDE 1
Key PK Parameters for Newer Antipsychotics[4]

Drug	Principal enzyme	$t_{1/2\ (hours)}$	Bioavailability	T_{max}
Aripiprazole	2D6≥3A	75	87%	3–5
Clozapine	1A2	16	70%	1–4
Olanzapine	1A2	30	60%	6
Risperidone	2D6	3	70%	1–2
9-OH RIS	–	24-28	–	–
Quetiapine	3A	7	<20%	1–2
Ziprasidone	aldehyde oxidase >> 3A	7	60%	5

The half-life of antipsychotics varies greatly. Shorter half-life medications, such as quetiapine and ziprasidone, have a 7–12-hour half-life. Risperidone has a 3-hour half-life, but it is metabolized to 9-hydroxy risperidone (paliperidone), which has a 24–28-hour half-life, while olanzapine has a 30-hour half-life. The longest half-life, about 3 days, is seen with aripiprazole.[4]

A meta-analysis, designed to detect the near-maximal effective antipsychotic dose, found that the near-maximal dosages (ie, the threshold dose necessary to produce all or almost all the clinical response) of all first line antipsychotics was somewhat lower in the analyzed, randomized controlled trials than what clinicians would use for chronically-ill patients.[6] The near-maximal dosages of second-generation antipsychotics (SGAs) were: olanzapine 16 mg, risperidone 4 mg, aripiprazole 10 mg, quetiapine 150–600 mg, and ziprasidone 120-160 mg.[6]

In terms of real life dosing, finding the optimal dose that leads to sufficient efficacy, without reaching the threshold of EPS or akathisia, depends first upon the consideration of a number of pharmacologic variables. But, in patients not reaching efficacy who do not develop EPS, the physician should check for and ensure appropriate levels of adherence, and consider increasing the dose until efficacy is reached or side effects become dose limiting.

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Pharmacologically-Informed Antipsychotic Switching

Switching strategies should be informed by the clinical situation, as well as the pharmacology of the pre-switch and the post-switch antipsychotic. Regarding clinical situations, there are five broad categories: 1) Adverse-effect switch: a stable patient has developed side effects that do not require an emergent/fast switch; 2) Efficacy switch: the patient's psychiatric symptoms are not adequately covered by the prior antipsychotic. A faster action is typically required; 3) Mixed adverse effect and efficacy switch: since both adverse effect(s) and inefficacy need to be addressed, the more clinically pressing aspect will generally guide the switch strategy; 4) Non-adherence switch: consider supervised medication intake, as well as orally disintegrating medications or intramuscular long-acting formulations; 5) Treatment-refractory patients: this usually involves a switch to clozapine.

In addition to the clinical scenario, the pharmacodynamic and pharmacokinetic profiles of the pre- and post-switch medications are important in choosing the appropriate switch strategy. The pharmacodynamic profile has to do with the receptor affinity—how tightly the medication binds to specific receptors. Slide 2 shows the specific binding affinities of selected antipsychotics to relevant neuroreceptors, with lower numbers indicating tighter binding. The more the relative receptor affinity compared to dopamine (ie, drug binding to that receptor more tightly or less tightly than to dopamine) differs between the pre- and the post-switch antipsychotic, the more care must be taken, as pharmacodynamic rebound phenomena can otherwise complicate the switch (Slide 3).

For example, when switching from a tightly binding anticholinergic or antihistaminergic medication (eg, olanzapine, quetiapine, clozapine) to one with less anticholinergic or antihistaminergic affinity (eg, aripiprazole, risperidone, ziprasidone), often transient rebound anxiety, insomnia, agitation and restlessness can occur. In addition, when switching from a tighter D_2 binding agent to a looser-binding agent (eg, from risperidone to clozapine or quetiapine) or, particularly, to a partial dopamine agonist (eg aripiprazole) dopamine rebound symptoms, such as often transient worsening of psychosis, mania or aggression/agitation, can occur. A pharmacokinetic dopamine rebound may also occur when switching from a short half-life antipsychotic to a longer half-life antipsychotic (Slide 1).[4]

SLIDE 2

Approximate Receptor Binding Profiles and Half-Life of Selected Atypical and Typical Antipsychotics[7]

Receptor	ARI	OLA	PAL	RIS	QUE	ZIP	CLO	HAL	PER
*Receptor Binding Affinity Expressed as Equilibrium Constant (Ki)**									
D_2	0.66†,‡	20	2.8	3.8	770	2.6	210	2.6	1.4‡
5-HT_{2A}	8.7‡	1.5	1.2	0.15	31	0.1	2.6	61	5‡
α_1	26	44	10	2.7	8	2.6	6.8	17	10
α_2	74‡	280	80‡	8	80	154	158	600	500
H_1	30‡	0.1	3.4	5.2	11	4.6	3.1	260	8
M_1	>1,000‡	2.5‡	>10,000‡	>10,000‡	120‡	300‡	1.4‡	>10,000‡	>1,000
Pharmacokinetic Profiles: Half-life									
$t_{1/2}$, h	72	30	24	3	7	7	16	20	8–12

Data based exclusively on human brain receptors; *Data represented as Ki (nM), ie, nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (ie, lower number equals stronger receptor affinity/binding. †Partial agonism; ‡Data from cloned human brain receptors; ARI=aripiprazole; OLA=olanzapine; PAL=paliperidone; QUE=quetiapine; ZIP=ziprasidone; CLO=clozapine; HAL=halperidol; MOL=molindone; PER=perphenazine

SLIDE 3

Pharmacodynamic Side Effects During Switching: Acute Rebound from Complementary Blockade of Previous Antipsychotic[8]

Receptor	Blockade	Dopamine Rebound Symptoms
D_2	Antipsychotic, antimanic, antiaggressive, EPS/akathisia, increased prolactin, tardive dyskinesia	Agitation, akathisia, mania, psychosis, withdrawal dyskinesia
H_1	Anxiolytic, anti-EPS/akathisia, calming, sedation, sleep-inducing, weight gain	Agitation, anxiety, EPS/akathisia, insomnia
M_1 (central)	Anti-EPS/akathisia, cognition, dry mouth, memory	Agitation, anxiety, confusion, EPS/akathisia, insomnia, psychosis, sialorrhea
M_{2-4} (peripheral)	Blurry vision, constipation, hypertension, tachycardia, urinary retention	Bradycardia, diaphoresis, diarrhea, hypotension, nausea, syncope, vomiting
5-HT_{2A}	Anti-EPS/akathisia, antipsychotic	EPS/akathisia, psychosis

EPS=extrapyramidal symptoms.

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The abrupt switch has the greatest potential for rebound and withdrawal phenomena. Even the conventional cross-titration can lead to problems when the pre-switch antipsychotic has a shorter half life and/or blocks more tightly cholinergic, histaminergic or dopaminergic receptors than the post-switch antipsychotic. Rebound phenomena can be minimized by avoiding abrupt or fast switching when the pre- and post-switch receptor affinities and/or half-lives differ considerably. Instead, an overlapping or "plateau" switch should be used. This consists of decreasing the pre-switch antipsychotic slowly (eg, 25% to 50% every 5 half-lives) and only after the post-switch antipsychotic has reached steady state (ie, ≤5 half lives on target dose). Adding calming medications during the switch period, such as benzodiazepines, antihistamines or sleep aides, can also minimize rebound phenomena.

A meta-analysis comparing antipsychotic switch strategies did not find outcome differences to be dependent upon whether the pre-switch antipsychotic was discontinued gradually or abruptly, or whether the post-switch antipsychotic was initiated gradually or abruptly.[9] These studies were, however, inpatient trials with 24-hour supervisions, and usually undisclosed amounts of benzodiazepines were allowed. Moreover, none of the studies investigated true "plateau switch" strategies, which recent trials have shown to lead to fewer dropouts due to adverse effects than more abrupt switch procedures.[10,11]

Augmentation Strategies

When a patient demonstrates insufficient or, particularly, only partial treatment response, augmentation strategies of antipsychotics, either with a second antipsychotic or with a non-antipsychotic, are frequently employed.

There are several important reasons for employing antipsychotic polypharmacy.[12] These include ongoing or aborted cross-titration, hopes of enhancing or hastening antipsychotic efficacy, targeting different symptoms (eg, agitation, negative symptoms) or symptom domains (eg, insomnia, anxiety, depression) that are insufficiently addressed by the first antipsychotic. Antipsychotic polypharmacy can, however, also result from poor communication between services, family pressure or preferences, or prescriber habits. Antipsychotic polypharmacy is only endorsed by treatment guidelines after failure or refusal of clozapine.[13,14] Concerns include a higher than necessary total dosage, increased acute long-term side effects, drug-drug interactions, increased mortality or non-adherence rates, difficulty determining the cause and effect of the combination treatment, increased cost, and lack of evidence-base.

A recent meta-analysis of >1,200 patients from 19 randomized controlled studies found that antipsychotic co-treatment could be helpful in certain circumstances.[15] However, the authors concluded that the data base was insufficient to make treatment recommendations, as most of the studies included clozapine, making it difficult to generalize these findings to the much more prevalent practice of combining two non-clozapine antipsychotics.

A number of non-antipsychotic augmentation strategies have also been tested in schizophrenia patients with insufficient response to antipsychotic monotherapy. Of these, lithium,[16] carbamazepine,[17] and beta blockers[18] were not superior to placebo when added to antipsychotic. Similarly, benzodiazepine[19] and valproate augmentation[20] also did not show long-term superiority compared to placebo, although both agents might speed up the initial response. Although two large-scale studies showed no superiority of lamotrigine augmentation of antipsychotics compared to placebo,[21] a meta-analysis demonstrated significant superiority regarding global ratings of psychopathology, positive and negative symptom change, as well as study-defined response when outcomes of patients were combined in whom lamotrigine was added to clozapine.[22] This, however, has not been verified in a prospective study.

Electroconsulvie therapy augmentation has also been shown to be superior, both for acute efficacy and in maintenance treatment, when added to antipsychotic monotherapy in patients who have failed antipsychotic monotherapy.[23]

One meta-analysis suggested that augmentation of antipsychotics with antidepressants may be more helpful than placebo for schizophrenia patients with predominantly negative symptoms.[24] Larger, validating studies are needed, however, and specific effects on negative symptoms need to be distinguished from proven effects of antidepressants on depressive symptoms in schizophrenia patients.[25]

Conclusion

Exclusion criteria and randomization bias limit the dosage recommendations based on registration and labeling trials.[26] Switching and dosing can be optimized, taking into consideration the receptor binding potential, as well as the half-life of both the pre- and post-switch antipsychotic. In general, abrupt switching of antipsychotics is neither advisable nor necessary.

Temporary rescue medications can help during the initial switch period minimizing potential rebound or destabilization phenomena, although often unspecified rescue medications limit recommendations from randomized switching studies.

Case Report

Ms. L is a 37-year-old female with schizophrenia since age 23. At her last inpatient admission she was treated with olanzapine 20 mg. Lithium 900 mg was added for mood symptoms. During the following 9-month outpatient phase she had mild residual positive and relevant negative symptoms. Ms. L complained of a 7-kg weight gain, and daytime sedation. Her fasting triglycerides level was 265 mg/dL; glucose: 95 mg/dL. The decision was made to switch to aripiprazole.

Aripiprazole 10 mg was started, with taper of olanzapine over 1 week. Ms. L presented on day 10 with agitation, restlessness, insomnia, worsening of psychosis (voices telling her that an old colleague has gotten a group of people together that want to "destroy her life"). Olanzapine 20 mg was restarted due to "failure of aripiprazole to maintain efficacy of olanzapine." Ms. L experienced further weight gain (4 Kg), daytime sedation and an elevated triglyceride levels: 280 mg/dL, and glucose: 116 mg/dL.

The preceding case report highlights several potential problems and pitfalls with switching antipsychotics. First, the initial target dose of aripiprazole was too low. Importantly, olanzapine was discontinued too quickly. The second problem is the lack of overlap between a pre-switch antipsychotic with sedating, anticholinergic, and full antidopaminergic properties when switching to an antipsychotic with less sedating and anticholinergic properties,

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partial D_2 agonism and a longer half life. Third, rebound phenomena (agitation, insomnia, anxiety, mania) were mistaken for lack of efficacy of aripiprazole, and there was a failure to treat rebound phenomena with transient adjunctive medications.

In a second treatment scenario, the decision was made to reattempt a switch to aripiprazole. Aripiprazole was added at 15 mg/day for 1 week, then increased to 20 mg/day. Only after 2 weeks of aripiprazole 20 mg/day, olanzapine was reduced by 5 mg every 7 days ("plateau switch"). Ms. L remained stable off olanzapine with no more sedation, was more active, and experienced 3 kg weight loss; triglycerides: 155 mg/dL, glucose 100 mg/dL.

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