Real-Life Switching Strategies With Second-Generation Antipsychotics

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In last month's ASCP Corner,[1] the issue of real-life dosing of second-generation antipsychotics (APs) in patients showing an inadequate response to recommended doses was discussed. The article focused on reasons why the dose ranges derived from premarketing registration trials may not be generalizable to certain clinical populations that are systematically excluded from these important efficacy studies.

This month's column will examine different switch strategies of second-generation APs in patients showing an inadequate response to an appropriate trial with an AP, again addressing the question of generalizability of the results from randomized controlled trials comparing different switch strategies.

The increasing number of newer APs coupled with an often inadequate treatment response in chronically ill patients makes AP switching common in the treatment of severe mental disorders.[2,3] While several studies have investigated different switching strategies, data are sparse and conflicting[4]; therefore, no clear algorithmic approach has been established. Nevertheless, several authors have proposed a conservative approach, favoring more gradual switch strategies.[5,6] In clinical practice, however, clinicians may attempt less conservative strategies because of time and reimbursement constraints. For example, in a retrospective study of 60 patients switched to amisulpride, 89% of patients were switched abruptly.[5]

SWITCH STRATEGIES

Switching from one to another AP is often appropriate when patients achieve only partial or no relevant reduction in symptoms or when they show insufficient functional improvement. Other reasons include relapse despite compliance or intolerance due to significant side effects. The main goal when switching APs is to improve or, in stable patients, maintain the symptomatic and functional level while improving or, at least, not worsening tolerability of the treatment.[4,5]

Overall, 8 different switch strategies are conceivable, depending on how fast the second and the first agents are either introduced or stopped, respectively, and whether there is partial or full overlap between the agents:

1. Abrupt switch: Therapeutic dose initiation of the new AP and abrupt discontinuation of the first AP
2. Ascending switch: Gradual dose escalation of the new AP and abrupt discontinuation of the first AP
3. Descending switch: Therapeutic dose initiation of the new AP and gradual discontinuation of the first AP
4. Cross-titration: Gradual dose escalation of the new AP and gradual discontinuation of the first AP
5. Plateau switch: Therapeutic dose initiation of the new AP with *delayed* abrupt discontinuation of the first AP
6. Ascending plateau switch: Gradual dose escalation of the new AP with *delayed* abrupt discontinuation of the first AP
7. Descending plateau switch: Therapeutic dose initiation of the new AP with *delayed* gradual discontinuation of the first AP
8. Plateau cross-titration: Gradual dose escalation of the new AP with *delayed* gradual discontinuation of the first AP.

Potential Advantages and Disadvantages of Abrupt or Overlapping Switch Strategies

In general, strategies involving abrupt discontinuation have a higher risk for withdrawal symptoms, but they avoid confusion between concurrent dose changes with 2 medications and can help to eliminate the unwanted effects of the first agent more quickly. Therapeutic dose initiation of the second AP may bring about a faster onset of wanted action, but it can also be associated with more side effects.

Cross-titration and, particularly, plateau switch strategies may limit unwanted physiologic effects associated with a rapid onset of the newly started AP and/or of withdrawal phenomena associated with a rapid offset of the discontinued AP. These strategies can be confusing, however, and can be associated with higher rates of side effects, especially when adverse effects are shared between the 2 agents (e.g., sedation, orthostasis, extrapyramidal side effects, prolactin elevation, prolonged QT interval). Moreover, with overlapping strategies, patients may be less likely to follow instructions, thinking that 2 agents taken concurrently may be unnecessary or harmful. Therefore, patients require specific instructions, explaining that the concurrent treatment with 2 APs is intended to be temporary, aiming to minimize rather than to exacerbate side effects. Notwithstanding these intentions, overlapping switch strategies can increase the frequency of unnecessary polypharmacy in those cases when patients improve during the switch process and the switch is aborted.

Comparative Evidence Base of Different Switch Strategies

In the few controlled studies that have compared different switch strategies using APs,[6–9] the first 4 methods were investigated. In these studies, "gradual" discontinuation or escalation was generally defined as a 2- or 3-week period (i.e., 50% to 100% or 33.3% to 67% to 100% for the stepwise escalation strategies and 50% to 0% or 50% to 25% to 0% for the discontinuation phase).

No systematic data are available to assess whether an even slower dose reduction would be advisable when switching from conventional APs. In this scenario, overexpression of dopamine receptors could be expected, and more time may be necessary for a decrease not only in sensitivity but also in number of dopamine receptors to occur.

The overall consensus of the available randomized switch studies involving olanzapine,[7,8] ziprasidone,[6] and aripiprazole[9] is that the examined switching strategies are equally successful. However, each of these studies was industry-sponsored, which may have introduced a bias toward designing studies that were likely to show feasibility of any switch strategy to the AP in question.

On the other hand, the need for an "individualized approach" has also been acknowledged.[5,10] Such an approach is readily understandable when focusing on side effects that are either the cause for the switch or that can occur during the AP change. A switch may have to be accelerated in the presence of serious adverse events due to the first AP, such as diabetic ketoacidosis, pancreatitis, agranulocytosis, or neuroleptic malignant syndrome. On the other hand, emergent withdrawal dyskinesia or worsening of symptoms after abrupt discontinuation or taper of the first AP may dictate reintroduction of the first AP, followed by a descending switch, cross-titration, or any plateau switch method.

As discussed in last month's column,[1] sampling and cohort biases in existing switch studies may limit the applicability of their results to individual patients. Further limiting the generalizability of these trials is the fact that reasons for switching were not sufficiently addressed. It may be relevant for outcomes of different switching strategies whether patients were switched due to intolerance or lack of efficacy or

both. Most importantly, the allowed use of (mostly poorly characterized) rescue strategies, such as liberal doses of benzodiazepines during the first 7 to 10 days, may obscure problems that can arise from dopamine, histamine, and/or cholinergic withdrawal when switching APs abruptly in clinical settings. Clinical manifestations can include primary symptom exacerbation, agitation, insomnia, anxiety, or withdrawal-emergent dyskinesia or akathisia, all of which may occur in particular in outpatient settings, where benzodiazepines are used more cautiously. Finally, the unique pharmacology of specific second-generation APs may require individualized switching strategies based on characteristics not only of the individual patient but also of the individual APs used.

Considerations About Initiation of the Second Antipsychotic

When switching to clozapine, the increase will always have to be gradual because of the accentuated risk for orthostatic, cardiac, vegetative, and hematologic side effects associated with rapid dose escalation. When the first AP is also highly sedating or orthostatic in nature, a plateau strategy may also not be feasible.

Similarly, a more gradual dose escalation strategy may be necessary for risperidone because of the risk for extrapyramidal side effects, particularly dystonic reactions (except when combined initially with prophylactic anticholinergic treatment). The same is true for aripiprazole because of its potential to cause nausea, vomiting, or initial restlessness when initiated at full doses.

By contrast, when switching to olanzapine, quetiapine, or ziprasidone, one may want to use a more rapid dose escalation to achieve rapid efficacy and/or minimize side effects. Quetiapine may actually have a greater liability for sedation and orthostasis when increased gradually (i.e., reaching 400 mg over the course of 5 days).[11] Further, ziprasidone and quetiapine appear to require reaching a threshold to exhibit sufficient dopamine blockade for antipsychotic and antimanic efficacy, and to avoid rebound agitation or psychosis or withdrawal dyskinesia in some patients after reducing or stopping the first AP.

Considerations About Discontinuation of the First Antipsychotic

The fact that plateau switch strategies have not been considered widely may be because until recently most APs have had relevant sedating qualities. Since the introduction of ziprasidone and aripiprazole, reports have implicated these agents as having "activating" effects or causing worsening of psychosis.[12–14] *Activation*, however, is an imprecise term. More accurately, one needs to assess for presence of reemerging psychosis or agitation, akathisia, anxiety, or insomnia.

An alternative or complementary explanation for at least some of these reports could be that these 2 agents have markedly reduced histaminic and/or cholinergic affinity compared with most other APs. When switching abruptly or too quickly from a sedating, anticholinergic drug to ziprasidone or aripiprazole, one can induce a withdrawal syndrome that can mimic reemergence of psychosis or agitation, akathisia, anxiety, or insomnia, but more precisely represents rebound psychosis or agitation, or withdrawal akathisia, insomnia, or anxiety. To avoid this scenario, plateau switch strategies can be helpful, as they allow ziprasidone or aripiprazole to build up and achieve sufficient dopaminergic blockade before a more antihistaminic or anticholinergic medication is withdrawn.

For 2 other reasons, using an overlapping and, ideally, plateau method may be relevant for a switch to aripiprazole. First, the partial dopamine agonism may vary depending on the degree of dopamine blockade exerted by the first AP. When the first AP is withdrawn too quickly, before aripiprazole has built up centrally, it is conceivable that aripiprazole may exert exaggerated dopamine agonistic activity when facing an environment of up-regulated dopamine receptors.[15] Second, depending on the initial dose and titration, the 72-hour half-life of aripiprazole may require up to 7 to 10 days of treatment to achieve adequate antidopaminergic activity to compensate sufficiently for a rapid reduction in dopamine blockade when the first agent is withdrawn abruptly.

Even using cross-titration from a shorter half-life AP to aripiprazole, as opposed to a plateau switch strategy, can conceivably still create a window of suboptimal dopamine blockade in addition to the potential withdrawal/rebound from antihistaminic and anticholinergic blockade, which, clinically, can lead to "activating" side effects.

CONCLUSIONS

Design issues, patient selection strategies, and study procedures limit the generalizability of switch studies that may aim for equal efficacy of the examined strategies by allowing for liberally dosed rescue medications during the vulnerable period of the first 7 to 10 days of the switch. However, particularly benzodiazepines may not be prescribed the same way in clinical settings due to concerns about their abuse potential, paradoxical activation at the extremes of age, or withdrawal symptoms if rapid discharge to a less restrictive setting leaves insufficient time to properly taper sedatives. In addition to changes in brain physiology, the patient's potential anticipatory anxiety about treatment changes may accentuate problems that can be seen during AP switching when benzodiazepines or antihistamines are not used routinely. Besides interindividual patient and concurrent psychotropic treatment differences, variability in the pharmacologic profile of specific second-generation APs may call for different switch strategies depending on the relative degree of antidopaminergic, antihistaminergic, and anticholinergic blockade of each of the APs involved in the switch.

Additional research is needed to inform treatment guidelines and algorithms that will guide clinicians regarding the safest and most effective switching strategies involving specific patient groups and APs.

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