The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Adverse events associated with switching antipsychotics

Antipsychotics are the first-line agents for managing schizophrenia and related disorders. As with other chronic illnesses, clinicians must often decide whether to switch a patient's current medication to try to improve treatment response, reduce intolerable side effects and improve quality of life and functioning. Unfortunately, guidance for switching among antipsychotics is lacking, as minimal clinical research on switching strategies exists.

During a switch, patients often experience adverse events that require monitoring. These events are the result of a complex pharmacology in which antipsychotics target various receptor subtypes (e.g., D_2, 5-HT_{2A}, M_1, α_1, H_1) with varying degrees of affinity. Often, long-term antagonism of these receptors results in physiologic counter-adaptations, such as receptor upregulation. For example, if a patient switches too quickly from an antipsychotic with high affinity for a given receptor to one with low affinity, rebound and withdrawal symptoms can develop. Conversely, switching too quickly from an antipsychotic with low receptor affinity to one with high affinity can exceed the body's ability to adapt to the medication and result in receptor-related adverse events. It is recommended that clinicians switch medications gradually to avoid adverse effects. The method (e.g., cross-taper) and duration of switching depend on many variables, including the receptor profile, receptor affinity and the pharmacokinetic parameters of each antipsychotic.[1,2] In cases of a significant adverse event, the only option may be to abruptly switch antipsychotics.

Overstimulation of mesolimbic D_2 receptors likely contributes to the expression of psychosis. Switching from low- to high-affinity D_2 antagonists (e.g., quetiapine to haloperidol) can result in dyskinesias, parkinsonism, akathisia and acute dystonias. In these cases, clinicians should decrease the dose of the high-affinity agent and titrate more slowly. If akathisia persists, β-blockers or benzodiazepines may improve symptoms. Conversely, when switching from high- to low-affinity D_2 antagonist, patients may experience breakthrough psychosis, withdrawal dyskinesias and akathisia that may be indistinguishable from agitation. Tapering of the high-affinity agent should be slowed to allow more time for receptor adaptation.

Second-generation antipsychotics also exert their effects in part through the 5-HT_{2A} receptor. When switching from a drug with high affinity for 5-HT_{2A} to one with low affinity (e.g., olanzapine to quetiapine), rebound effects can include agitation, diaphoresis, fever, tremor and confusion. Slow titration over a few weeks should mitigate the occurrence of these adverse events.

Cholinergic M_1 receptors control salivation, smooth muscle contractions in the digestive and urinary tracts, memory and cognition. Switching from a low to a high-affinity M_1 antagonist (e.g., risperidone to olanzapine) can result in memory and cognitive impairment, dry mouth, constipation and urinary retention. Sugarless, hard candy may alleviate dry mouth, and increasing water and fibre may relieve constipation. Switching from a high- to a low-affinity drug can result in a cholinergic rebound with malaise, nausea, vomiting, diarrhea, sialorrhea, extrapyramidal symptoms and akathisia. A low-dose anticholinergic may be necessary to control such effects during a switch.

Adrenergic α_1 receptors control vascular smooth muscle contraction. Orthostatic hypotension may be a concern when switching from a low- to a high-affinity α_1 antagonist (e.g., olanzapine to clozapine). Conversely, switching from a high- to a low-affinity drug may result in rebound hypertension, tachycardia, tremor and restlessness. Blood pressure should be monitored regularly during the switch.

Many antipsychotics block H_1 receptors, and switching to a high-affinity drug (e.g., ziprasidone to clozapine) may result in sedation, increased appetite and weight gain. Patients should be informed of these potential effects and the importance of a balanced diet and physical activity. Switching from a high- to a low-affinity H_1 blocker may result in insomnia, agitation, anxiety, and akathisia. A sedative and/or anxiolytic may alleviate these effects.

Owing to the diverse receptor profile of antipsychotics, many adverse events may be observed when switching medications. Clinicians should be cautious and closely monitor patients for potential adverse events during the switch. There is a strong need for more clinical research on this topic and for additional resources to help clinicians implement optimal switching strategies to reduce patient discomfort.

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