Dose Modification Considerations With Atypical Antipsychotics

Finding the minimum effective dose of an atypical antipsychotic is an important strategy to balance long-term efficacy with patient needs.[1] Dose re-evaluation and subsequent reduction is commonly driven by clinical stabilization or the need to alleviate adverse effects; however, providers should be aware of medications that can alter atypical antipsychotic pharmacokinetic or pharmacodynamic properties.[1,2] Concomitant administration of these medications may lead to increased concentration or activity of the antipsychotic, which can increase the likelihood of undesired or dangerous adverse effects (eg, extrapyramidal reactions, seizures, QT interval prolongation, or neuroleptic malignant syndrome).[3,4]

Recognizing potential drug-drug interactions (DDIs) that affect antipsychotic metabolism can help prevent unintentional dose-related toxicity, support safer prescribing, and may decrease the likelihood patients will discontinue treatment due to adverse events.[3]

Drug-Drug Interaction Mechanisms and Increased Atypical Antipsychotic Exposure

The following mechanisms describe how DDIs can elevate atypical antipsychotic exposure and potentially increase the risk of adverse effects.

Pharmacokinetic Mechanisms

These mechanisms involve changes in the absorption, distribution, metabolism, or excretion of the drug, resulting in altered concentrations in the body.[2] The majority of pharmacokinetic DDIs involve alterations in phase I metabolism through cytochrome P-450 hepatic enzyme (CYP450) modulation.[5]

Hepatic cytochrome P450 inhibition
Some medications can inhibit CYP450 proteins in the liver, the primary metabolic enzyme responsible for biotransformation, thereby slowing clearance and increasing parent drug or active metabolite concentrations.[2]

Active drug transport system inhibition
Certain agents inhibit P-glycoprotein, normally responsible for drug efflux and transport at key anatomic barriers (eg, the blood-brain barrier and intestinal mucosa), thereby increasing central nervous system drug exposure.[6]

Plasma protein binding displacement
Drug interactions involving plasma protein binding can raise plasma concentrations of the displaced drug, but this usually has limited clinical impact because the increase in unbound drug enhances metabolism and clearance.[5]

Pharmacodynamic Mechanisms

These mechanisms involve the drug's effect at the receptor level or physiological pathway.[2]

Amplification of shared receptor pathways
Agents that act at the same receptor system or physiological pathway create additive or synergistic effects even when serum concentration is unchanged.[2]

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Atypical Antipsychotic Dose Adjustment Considerations for Drug-Drug Interactions

If a DDI is suspected, and switching to a non-interacting alternative is not feasible, dose adjustment decisions should be guided by modification of recommendations outlined in the antipsychotic's prescribing information.[1] These considerations apply both when adding a new interacting medication to an existing antipsychotic and when initiating an antipsychotic in a patient already receiving an interacting therapy.[6]

Key Takeaways

It is important for providers to understand DDIs in patients taking antipsychotics in combination with other medications.[3] Some concomitant medications can alter the metabolism of atypical antipsychotics, which may require dose modifications to help prevent adverse effects associated with elevated drug concentrations.[4]

When a potentially clinically significant interaction is identified or suspected, dosing should be adjusted in accordance with prescribing information.[1,6] This applies to patients already receiving atypical antipsychotics as well as those who are initiating treatment.

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