

DRUG DISPOSITION & PHARMACOKINETICS

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Drug-Drug Interactions Associated with Second-Generation Antipsychotics: Considerations for Clinicians and Patients

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ABSTRACT ~ Objectives: While not always clinically significant, patients with schizophrenia may be at risk for drug-drug interactions (DDIs) with second-generation antipsychotics. Second-generation antipsychotics are increasingly being used in a broader population of patients and, therefore, for those with comorbid illnesses, adjunctive treatments, or other diagnoses, the clinical significance of DDIs is increasing. This paper reviews currently available data concerning DDIs that occur between second-generation antipsychotics, and other medications or substances, when metabolized by the cytochrome P-450 (CYP) family of enzymes. This review will assess the clinical relevance of these interactions for physicians and patients with schizophrenia. **Methods:** EMBASE and MEDLINE searches were conducted (no date restrictions) using the keywords "drug-drug interactions," "atypical antipsychotics," "olanzapine," "ziprasidone," "quetiapine," "risperidone," "aripiprazole," "clozapine," "asenapine," "bifeprunox," and "paliperidone." **Principal observations:** Second-generation antipsychotics are primarily metabolized by CYP enzymes. When coadministered with inducers or inhibitors (psychotropic or non-psychotropic medications or substances) of CYP enzymes, antipsychotic plasma levels may be reduced or increased, respectively, as a result of DDIs. This can result in a reduced effectiveness of the antipsychotic, or an increased risk of adverse events, respectively. Drugs with a less clinically significant risk for DDIs are a more reliable treatment option for patients in whom drug plasma levels may fluctuate. **Conclusion:** Some of the currently available second-generation antipsychotics have a higher potential for DDIs. Agents with a reduced liability for DDIs may be safer treatments as the systemic drug concentration is less likely to seriously increase/decrease when other medications are knowingly or inadvertently co-prescribed or hepatic problems and drug abuse is present. *Psychopharmacology Bulletin. 2007;40(1):77-97.*

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INTRODUCTION

Profiling Patients with Schizophrenia

Patients with schizophrenia are highly likely to have comorbid medical and other psychiatric conditions (comorbidities),¹ often requiring multiple psychotropic or nonpsychotropic medications. Studies have shown that patients with schizophrenia are at an elevated risk of anxiety disorders, depression, cardiovascular disease, diabetes, hypertriglyceridemia, and infection with human immunodeficiency virus (HIV) and hepatitis C, thereby increasing the likelihood of polypharmacy.²⁻⁴ This risk of a comorbid medical diagnosis is further raised in certain populations with schizophrenia, such as the elderly, who are consequently more likely to be receiving concomitant therapy.^{5,6} Second-generation antipsychotics are now generally accepted as the first-line treatment for patients with schizophrenia; however, psychotropic polypharmacy is widely used either justifiably to treat comorbid conditions or, in some cases, due to poor prescribing practices.⁷⁻⁹ Specifically, antipsychotic polypharmacy (a combination of two or more antipsychotics) and pharmacological add-on therapy with benzodiazepines, antidepressants, and mood stabilizers are increasingly being used in patients with schizophrenia to treat various aspects of their illness.^{8,10}

In addition to medical comorbidities, it has also been shown that patients with schizophrenia are more likely to have comorbid substance abuse, such as alcohol, cannabis, cocaine, or nicotine dependence.¹¹⁻¹³ For example, results from a meta-analysis have demonstrated that, compared with the general population, patients with schizophrenia are more likely to start smoking, be heavy smokers, have high nicotine dependence, and be less likely to stop smoking.¹⁴ The risk of comorbid substance abuse is generally greater in younger populations.⁵ Patients with a dual diagnosis of schizophrenia and substance abuse are at particular risk for hepatic impairment; for example, alcohol abuse has been known for a some time to be associated with detrimental effects on the liver,¹⁵ which can result in a decrease in drug metabolism activity,¹⁶ and intravenous drug use can expose patients to hepatitis C and HIV infections and, therefore, increase the risk of hepatic disease.¹⁷ Hepatitis C has also been shown to reduce hepatic metabolic activity and, thus, drug clearance in this patient population. Moreover, recently published consensus recommendations for patients with schizophrenia and substance abuse point out that it is with this population and especially dual diagnosis patients with medical comorbidities that drug interaction concerns are critical.¹⁸ Comorbid substance abuse is, therefore, an important consideration in the development of a treatment regimen, since in addition to intrinsic deleterious effects on health and relationships, substance abuse



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can reduce adherence, efficacy of medication, and the optimal clinical outcome that patients could otherwise expect from their schizophrenia treatment.^{16,19-22}

