Newer and Older Antidepressants
A Comparative Review of Drug Interactions

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Summary

A large number of drug interactions involving antidepressants have been de­
scribed. Some of these are common to specific classes of antidepressant drugs,
while others are related to peculiar properties of individual compounds and vary
greatly from one compound to another within the same drug class.

In general, the broader the range of receptors and enzymes affected by a given
drug, the greater the potential for pharmacodynamic interactions. Older genera­
tion monoamine oxidase inhibitors (MAOIs) are particularly likely to cause
interactions. These can occur with a wide range of compounds including tyra­
mine-containing foods, alcohol (ethanol), opioids, sympathomimetic agents and
other antidepressant drugs [e.g. tricyclic antidepressants (TCAs) and selective
serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs)]. The more
recently developed reversible and selective inhibitors of monoamine oxidase-A, such as moclobemide, appear to carry a much lower risk of causing serious drug interactions.

TCAs affect several neurotransmitter systems, but to differing degrees. This may result in many clinically significant pharmacodynamic interactions, including the reversal of the hypotensive action of some centrally active antihypertensive agents and the potentiation of the effects of anticholinergic agents and CNS depressants. Important pharmacokinetic interactions with TCAs include induction of their metabolism by anticonvulsants and impairment of their elimination by metabolic inhibitors such as fluoxetine, fluvoxamine, antipsychotics and quinidine. Appropriate dosage adjustments may be required to minimise the potentially adverse effects resulting from these interactions.

Some second generation antidepressants do not differ greatly from TCAs in pharmacological profile and so may be involved in similar interactions. However, others have a more selective mechanism of action and a lower potential for drug interactions. This is especially true for the SSRIs, which cause fewer pharmacodynamic interactions than MAOIs and TCAs. Nevertheless, SSRIs may interact adversely with drugs that also affect serotonergic transmission (including lithium) and may inhibit selectively the hepatic enzymes involved in the metabolism of concurrently prescribed drugs such as TCAs, antipsychotics, carbamazepine, oral anticoagulants and β-adrenoceptor blocking agents. Fluoxetine and paroxetine, in particular, appear to be powerful inhibitors of CYP2D6, whereas fluvoxamine is a more potent inhibitor of CYP1A2.

Avoidance of unnecessary polytherapy, knowledge of the interaction potential of individual agents and careful individualisation of dosage based on close evaluation of clinical response are essential to minimise potentially adverse drug interactions among patients receiving antidepressant therapy.

The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were introduced in the late 1950s for the treatment of depressive disorders. However, these agents had some limitations in terms of efficacy and safety. In an attempt to overcome the limitations of these original agents, a new generation of antidepressant medications has been developed and marketed during the last 15 years. These compounds, termed the ‘second generation’, ‘atypical’ or ‘heterocyclic’ antidepressants, have supplemented, but not replaced, the older agents (table I).

The newer agents are structurally distinct from each other and are generally characterised by a more specific short term biochemical action than the older drugs. Among the newer agents, the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) are well differentiated in terms of mechanism of action and clinical profile. A balanced critical assessment of the efficacy and tolerability of newer versus older antidepressants has been made by Rudorfer and Potter. The present article will review and discuss drug interactions that can occur with antidepressants, and compare the interaction potential of newer versus older agents. Drug interactions are important clinical features, especially for compounds like antidepressants that are usually administered for long periods of time and are often prescribed in combination with other agents. Moreover, in addition to their well established use in depressive disorders, some antidepressant agents, in particular TCAs and SSRIs, have other potential therapeutic indications, such as the treatment of chronic pain, headache, obsessive-compulsive disorder, anxiety and eating disorders.