

Consultation-Liaison Psychiatry Drug-Drug Interactions Update

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New Column Debut

This is the first of, we hope, a series that will update pertinent issues regarding drug-drug interactions for consultation-liaison (C-L) psychiatrists. Reviews of articles, new medication profiles, and interesting tidbits are part of the focus of this new column. There are literally thousands of articles one can find on drug-drug interactions, and sorting through them is nearly impossible (and, we are under no illusions that we are omnipotent in this area). Additionally, the topic matures rapidly, making static publications such as review articles or monographs out of date by the time they are published. Therefore, it is our desire that "C-L Psychiatry Drug-Drug Interactions Update" will assist clinicians in updating their knowledge base on this topic by providing timely, informative, useful, and continuous updates for the C-L psychiatrist.

Synopses of Articles

**Jefferson JW, Griest JH:
Brussels sprouts and
psychopharmacology.
Psychiatric Clinics of North
America: Annual of Drug
Therapy 1996; 3:205-222**

We know this citation is 3 years old, so it is out of date, to some degree. However, drug-drug interactions are often

such a dry topic, and these authors are so good at making the subject enjoyable. The title alone is catchy. If reading reviews with pages of tables puts you to sleep, we highly recommend reading this relatively short, and pleasurable, review.

The beginning sections provide an overview of the cytochrome P₄₅₀ system (the authors also quickly explain the brussels sprouts connection). Jefferson and Griest do an excellent job at explaining the nomenclature and the evolutionary development of the system and its purpose. For example, they clarify how pesticide resistance or cancer risks can be influenced by induction, inhibition, or perhaps polymorphisms of cytochromes.

The rest of the article is organized well, discussing pertinent cytochromes and major, clinically relevant interactions. There are brief discussions on the problems with antihistamines, analgesics, and sedative hypnotics. The authors do not try to be so inclusive as to drag out the topic, but they hit the highlights with interesting anecdotes that get the reader interested in reading further. They even point out an example of how one could actually save money with expensive drugs by giving inhibitors to the expensive drug, thus lowering the dosage and cost (a potentially great scheme in today's cost-conscious climate). There are problems with this strategy, however, which we will address in the next discussed article. Overall, this article is a worthwhile read, particularly if this topic is either confusing or boring for you.

Keough A, Spratt P, McCosker C, et al: Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. N Eng J Med 1995; 333:628-633

Moore LW, Alloway RR, Acchiardo SR, et al: Clinical observations of metabolic changes occurring in renal transplant recipients receiving ketoconazole. Transplantation 1996; 6:537-541

Over the last 4-5 years, some have realized that you can use isoenzyme (cytochrome) inhibition to one's economic advantage. This cost-saving measure has been reported, for example, when clozapine is used with fluvoxamine (a potent inhibitor of clozapine metabolism) or with cimetidine (a lesser, but nevertheless, effective inhibitor of clozapine's metabolism).

But what's good for the goose is not always good for the gander. The two aforementioned articles give pause on using such an approach (besides the obvious concerns of blood monitoring and being careful not to make a patient toxic on the drug that has its metabolism inhibited). Essentially, Keough et al. demonstrated an 80% cost savings in cardiac transplant patients receiving the antirejection drug cyclosporine when given ketoconazole concomitantly over 1 year. However, Moore et al. report that giving ketoconazole long-term to renal transplant patients (realizing that we are mixing cardiac and renal patients, but in this case we believe there is no foul) lowers bone

density and may have other untoward metabolic effects. The reason for this is that ketoconazole potently inhibits $CYP_{450}III A_{3/4}$, which in addition to metabolizing many drugs (e.g., calcium channel blockers, many antidepressants and antipsychotics, to name a few) metabolizes products of our own metabolism, such as calcitriol and steroid hormones. Hence, the authors hypothesize that the new mix of these hormones, set off by introducing ketoconazole, may have deleterious effects on bone mineralization in transplant patients.

So when one reads in the future of saving dollars by inhibiting an isoenzyme or two, being cautious is warranted.

Citalopram in 1999 edition of Physician's Desk Reference

Gelenberg AJ: Citalopram (Celexa): SSRI No. 5. Biological Therapies in Psychiatry Newsletter 1998; 21:41-42

Scates AC, Doraiswamy PM: Focus on citalopram. Formulary 1998; 33:725-743

Citalopram is the newest selective serotonin reuptake inhibitor (SSRI). Your clinical experience and reading of the literature will help you decide where it belongs in your armamentarium to fight depression and other maladies. However, you may ask, "how does it fair with the other SSRIs and their inhibition profiles of the cytochrome P_{450} system?" The simple answer is "very well" in our opinion.

Essentially, citalopram does not inhibit $CYP_{450}III A_{3/4}$ and has weak (and probably clinically insignificant) inhibition effect on all the others. This is good news, since none of the other SSRIs has such a profile (although sertraline is weak at low dosages, it does have more relevant inhibition at high-dose ranges, such as 200 mg/day).

It is metabolized by $CYP_{450}III A_{3/4}$ and $CYP_{450}II C_{19}$, so inhibitors of these isoenzymes can raise citalopram levels.

Drugs that could raise citalopram levels include some azole antifungal agents, some macrolide antibiotics, nefazodone, cyclosporine, grapefruit juice, some protease inhibitors, and omeprazole. Also, since some ethnic groups lack $CYP_{450}II C_{19}$ (up to 20% of Japanese and 10% of African-Americans), one could expect that if such an individual were given both an inhibitor of $CYP_{450}III A_{3/4}$ along with citalopram, the person could end up having very high levels of citalopram.

Hence, if all other factors are equal, and you are concerned about drug interactions in a patient, citalopram is a good choice as an SSRI.

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