

## **Psychopharmacology Articles Case**

**The following articles are used in this case discussion:**

Antidepressants: Update on New Agents and Indications by Adrienne Ables, PhD and Otis Baughman III, M.D. from American Family Physician February , 2003, Volume 67, Number 3, pg. 547-554.

Current Psychotropic Dosing and Monitoring Guidelines 2002 by Alan F. Schatzberg and Charles DeBattista, DMH, MD from Primary Psychiatry, June 2002: 9(6): 34-48

### **Discussion Questions**

**(Please see assigned articles for reference)**

1. A 54 year-old healthy MWM presents to the clinic with a history of MDD recurrent X 20 years. Current symptoms include: depressed mood, anhedonia, poor appetite and initial insomnia. He takes Zoloft 150 mg daily X 3 months with partial benefit but has complaints of anorgasmia and erectile failure.
  - A. What is the mechanism for SSRI induced sexual dysfunction?
  - B. What would be the next step in evaluation?
  - C. What other options for treatment of depression would you consider and why?
  - D. If this patient had a history of seizure disorder, which antidepressant would be contraindicated?
  - E. If this patient reports a long history of problems with medication non-adherence, which antidepressants would you avoid and why?

- F. If this patient has a history of multiple overdoses in the past, which antidepressant classes would you avoid?
  
  - G. You change the patient to a different antidepressant and he responds well with no side effects, "I'm feeling the best I have in years!" How long would you continue him on the medication and why?
2. What would be the concern (i.e. side effects, toxicity) with taking the following medications together? How would you further evaluate and treat any resulting toxicity?
- A. Paroxetine and Desipramine
  
  - B. Phenelzine and Fluoxetine
  
  - C. Diphenhydramine and Amitriptyline
  
  - D. Carbamazepine and OCP's
  
  - E. Zispraside and Quinidine
  
  - F. Ketoconazole and Nefazadone

## G. Paroxetine and Warfarin

## **Know Drug Profiles to Avoid Ugly Interactions**

By Winnie Anne Imperio, Senior Writer  
Clinical Psychiatry News, May 2001

San Francisco- When coping with drug interactions, most of what physicians do is anticipation and prevention, Dr. David J. Greenblatt said in an industry-sponsored symposium at the annual meeting of the American Association of Geriatric Psychiatry.

It's important to know whether a drug being prescribed is a highly potent inducer, a highly potent inhibitor, or a potential victim drug with a narrow therapeutic index in which the effect of interaction is likely to be greater clinically, Dr. Greenblatt advised in the symposium sponsored by Forest Pharmaceuticals Inc.

When possible, choose a low-risk perpetrator within a drug class; that is, a drug that is not as likely to alter the effect of other drugs. For example, high-risk antidepressants include fluvoxamine, nefazodone, fluoxetine, and paroxetine. Low-risk antidepressants include sertraline, citalopram, venlafaxine, and mirtazapine.

Also, when possible, choose a victim drug (a drug that is affected by a perpetrator) with multiple parallel pathways of metabolism. If the drug is metabolized by just one pathway and that pathway is interrupted, plasma levels can increase as much as 10-fold. If the drug has multiple pathways of metabolism, it is easier to deal with clinically, said Dr. Greenblatt, chair of pharmacology and experimental therapeutics at Tufts University, Boston.

In order to sort through the continually increasing body of literature on drug interactions, it helps to have a basic understanding of the drug-metabolizing enzymes - the cytochrome P450 superfamily - he said. Of the seven principal P450 enzymes, the 2D6 and 3A enzymes mediate clearance of several psychotropic and cardiovascular medications. (See tables)

Though 2D6 is low in abundance in the liver, it has a high affinity for its substrates. Because of a genetic polymorphism, 5% - 10% of the population fails to express active enzyme. These individuals are known as poor metabolizers. Considering the likelihood of adverse reactions, the prevalence of poor metabolizers, and cost effectiveness, it is not clear whether every patient's phenotype should be determined before giving a 2D6 substrate, Dr. Greenblatt said.

An alternative to phenotyping is to be aware and use clinical judgment, he advised. When starting a patient on a 2D6 substrate, start with low doses and monitor plasma levels. Poor metabolizers will respond to very low doses.

Some cardiovascular and psychotropic medications also are metabolized by 3A enzymes, which are highly abundant in both the liver and the gastrointestinal tract. Though no genetic polymorphism exists, there is great variability in the population in the ability to metabolize 3A substrates.

Substrates of the 3A enzymes can be divided into complete and partial substrates. Complete substrates are metabolized solely by 3A enzymes, making them more vulnerable to drug interactions, while partial substrates are only partially dependent on these enzymes for metabolism. (See table)

The concern over drug interactions has peaked in 2001 because drug development has flourished

over the past decade. Patients with serious illnesses are living longer and receiving multiple medications. Also, newer and highly effective medications - such as antiretroviral agents, antifungal agents, tuberculous medications, newer antidepressants, and antineoplastic agents - increasingly have secondary effects on drug metabolism.

Despite this, the significance of drug interactions has been greatly overblown in the emotional literature, medical journals, and the lay media, Dr. Greenblatt said.

“When you look at the prevalence of polypharmacy in clinical practice, the statistical possibility of drug interactions is very large, but given the number of possible interactions, the number of actual interactions is small.”

The most common interaction between drugs is no interaction, he said. Occasionally, clinically unimportant interactions occur in which the interaction is small in magnitude and undetectable, or the “noise” in the variability of the therapeutic response is much larger than any effect that could be attributable to a drug interaction.

<b>CYP3A Substrates, Inhibitors, and Inducers</b>		
<b>Substrates</b>	<u><b>Complete</b></u> Short half-life benzodiazepines Buspirone Trazodone Nefazodone Cyclosporine Statins Triptans Calcium antagonists Quinidine Protease inhibitors Sildenafil Quetiapine	<u><b>Partial</b></u> Zolpidem Amitriptyline Imipramine Sertraline Citalopram Diazepam Clozapine Mirtazapine
<b>Inhibitors</b>	<u><b>High Risk</b></u> Ketoconazole Itraconazole Nefazodone Ritonavir (acute) Erythromycin Clarithromycin Calcium antagonists	<u><b>Moderate Risk</b></u> Fluconazole Fluvoxamine Fluoxetine Grapefruit juice Other HIV protease inhibitors Delavirdine Cimetidine
<b>Inducers</b>	Rifampin Barbiturates Carbamazepine Ritonavir (chronic) Nevirapine St. John's wort	

<b>CYP2D6 Substrates and Inhibitors</b>	
<u><b>Substrates</b></u> Desipramine Nortriptyline Venlafaxine Paroxetine Codeine Tramadol $\beta$ -blockers (some) Antiarrhythmics (some) Dextromethorphan	<u><b>Inhibitors</b></u> Quinidine Fluoxetine/Norfluoxetine Paroxetine Terbinafine Perphenazine Ticlopidine