The Carlat Psychiatry Report

A CME publication

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

VOLUME 9, NUMBER 2 WWW.THECARLATREPORT.COM FEBRUARY 2011

IN THIS ISSUE

Focus of the Month:
Drug-Drug Interactions

Learning objectives for this issue: **1.** Define pharmacodynamic and pharmacokinetic drug interactions. **2.** Describe common drug interactions related to the cytochrome P450 enzymes. **3.** Explain frequent drug interactions psychiatrists should be aware of. **4.** Understand some of the current findings in the literature regarding psychiatric treatment.

Drug Interactions in Psychiatry: A Practical Review

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Dr. Goren and Dr. Carlat have disclosed that they have no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

During the heyday of the SSRI wars, every pharmaceutical sales rep was educating us about drug interactions. Zoloft and Celexa reps would gloat about how "clean" their drugs were, while Paxil reps would try to shift the conversation to a discussion of social anxiety disorder. Now that most SSRIs have gone generic, the reps have stopped pushing them, and we have been hearing a lot less about drug interactions—but that doesn't mean they've gone away.

In fact, drug interactions are common in psychiatry. The task of keeping track of interactions has become less daunting with the advent of free software from companies like Epocrates (www.epocrates.com) and Medscape (www.medscape.com), which allow you to type in every drug your patient is taking and find out if there is a potential interaction.

But there are various problems with such computerized databases. For one, they tend to be overly inclusive, often listing every conceivable interaction, no matter how unlikely. For example, citalopram (Celexa), an SSRI considered by most of us to be a pretty safe choice in combination with just about any drug, looks pretty dangerous in the Epocrates database. Cross referencing it with just about any mood stabilizer, antipsychotic, or antidepressant yields a host of red flag messages, often involving an increased risk of serotonin syndrome, neuroleptic malignant syndrome, and that apparently common citalopram side effect—SIADH!

Second, since your computer has not personally evaluated your patient, it can't know what kinds of symptoms to look for, and which potential interactions to focus on. For example, if your patient is jittery and tremulous after having started an SSRI, you will know to focus on drugs that can cause serotonin syndrome—but your computer will not.

In this article we'll survey those drug interactions that are most likely to be-

Continued on Page 2

 Continued from Page 1

come troublesome in day to day psychiatric practice. But first, we'll begin with a primer on the two large categories of drug interactions possible: pharmacodynamic and pharmacokinetic.

Pharmacodynamic Interactions

Pharmacodynamic interactions operate at the level of neurotransmitters and mechanisms of action. For example, clonazepam (Klonopin) makes people sleepy by stimulating GABA receptors. Quetiapine (Seroquel) also makes people sleepy, probably by blocking histamine receptors. Combine the two, and patients become really sleepy. Other times, pharmacodynamic interactions may cause two drugs to oppose one another. Antipsychotics work by blocking dopamine receptors. Stimulants enhance dopamine release. So what happens when they are used together? Well, the answer depends on many different factors (eg, tightness of drug-receptor binding, relative concentrations of the drugs at the site of action, etc). So in some patients, the antipsychotics may, at least theoretically, be antagonized by the pro-dopamine effect of stimulants. (For a more detailed discussion of this issue, see http://bit.ly/f5YLkH.)

While we may not realize it, we account for pharmacodynamic interactions on a regular basis in our clinical practices by doing things like lowering doses, choosing alternative medications, and increasing visit frequency. For example, when a patient who has been on long term clonazepam for generalized anxiety presents with depressive symptoms, we generally try to avoid sedating antidepressants in order to prevent daytime sleepiness.

Here's a fancier example of using knowledge of pharmacodynamics to our advantage: Levodopa is a good treatment for Parkinson's disease, but it can cause psychosis by revving up dopamine. Rather than decreasing the dose of levodopa, clinicians often turn to quetiapine to antagonize levodopa's pro-psychosis effect, while sparing its positive effects on movement. In our experience, many psychiatrists consider these adjustments as simply the "art of prescribing," not realizing just how skilled they are at understanding and managing pharmacodynamic interaction.

Pharmacokinetic Interactions

Pharmacokinetic interactions are hard to predict since they are unrelated to the pharmacologic action of drugs. The effects of the interaction depend on where and when two or more drugs come in contact during drug processing.

Drugs can interact with one another at four different junctures:

1) absorption (that is, the process of getting the drug into the bloodstream),
2) distribution (ferrying drugs to different tissues once they've been absorbed),
3) metabolism (dismantling drugs into simpler components), or
4) excretion (sending drugs into the sewage system).

We'll discuss each one in turn, focusing on some common examples in psychopharmacology.

Absorption. Drug-food, rather than drug-drug, interactions are most relevant during absorption. For example, ziprasidone (Geodon) absorption is halved when taken without food, which is why we instruct our patients to take this drug after a full meal (at least, we should be doing this!). Food also speeds absorption of both sertraline (Zoloft) and quetiapine, but only by 25% or so, usually not enough to be clinically relevant. Meanwhile, food famously slows absorption of erectile dysfunction drugs such as sildenafil (Viagra) and vardenafil (Levitra)—but not tadalafil (Cialis).

Distribution. Valproic acid (Depakote) is highly protein bound, and it is only the unbound portion (the "free fraction") of the drug that has a therapeutic effect. Aspirin is also highly protein bound, so if your patient combines the two drugs, the aspirin will kick some of the valproic acid off its proteins, causing the free fraction of the drug to increase. Standard valproic acid levels do not account for the difference between free and bound fractions, so your patient's serum level might appear normal, but the actual functioning valproic acid can be very high, potentially causing side effects. One way to account for this interaction is to order a free valproate level (with the normal therapeutic range being about 5 mcg/ml to 10 mcg/ml, much less than the total valproic acid therapeutic range of about 40 mcg/ml to 100 mcg/ml).

Excretion. Lithium, unlike almost all other drugs in psychiatry, is not metabolized by the liver. Instead, it is excreted unchanged by the kidneys. Because of this, various drugs that affect kidney function can severely affect lithium levels. Coffee, for example, speeds up kidney functioning and can lead to lower lithium levels. On the other hand, both ibuprofen (along with other NSAIDs) and ACE inhibitor can decrease lithium excretion and lead to toxicity.

Liver metabolism. Most drug-drug interactions take place in the liver, where drugs are processed in order to render them water soluble, which allows the body to more easily excrete them, either in the urine or feces. There are two phases of liver metabolism. Phase I involves the famous cytochrome P-450 enzymes, or CYP450. These enzymes attack drugs in a variety of ways, such as "hydroxylation" (adding a hydroxyl group), "dealkylation" (taking away an alkyl group), and several others. Unfortunately for those of us trying to remember drug interactions, there are many subfamilies of CYP450 enzymes, including CYP 1A2, 2C19, 2D6, and 3A4. Phase II metabolism continues the process of biotransformation, relying mainly on glucuronidation—which is rarely a factor in drug interactions in psychiatric practice.

Practical Implications of Drug-Drug Interactions

To understand drug-drug interactions, you'll need to refamiliarize yourself with some basic terms. Drugs are "substrates" of specific enzymes. An "inhibitor" is a drug that binds more tightly to an enzyme than the current resident. This "victim" drug then gets stuck in a game of metabolic musical chairs as it scurries around looking for a free enzyme system to break it down. Since this drug is not getting metabolized as quickly as it otherwise would, its serum levels become higher than expected.

"Induction" happens when the inciting drug stimulates the production of extra enzymes. With more enzymes around,

Continued on Page 3

Common Drug Interactions for Psychiatric Medications

CYP450 Family	Inducers	Inhibitors	"Victim Drugs" (Substrates)	Symptoms When Inhibited	Symptoms When Induced
1A2	Carbamazepine Cigarette smoke	Fluvoxamine Ciprofloxacin Norfloxacin Ketoconazole	Asenapine	Insomnia/EPS	Psychosis
			Caffeine	Jitteriness	Withdrawal headaches
			Clomipramine	Seizures/arrhythmia/anticholinergic effects	Depression
			Clozapine	Seizures/sedation/anticholinergic effects	Psychosis
			Duloxetine	Increased blood pressure	Depression
			Mirtazapine	Somnolence	Depression
2C9/19	Ginkgo biloba	Fluoxetine Fluvoxamine Carbamazepine Modafanil Oxcarbazepine Valproate Fluconazole	Diazepam	Intoxication	Anxiety/seizures
			Tricyclics	Seizures/arrhythmia/anticholinergic	Depression
			Oral hypoglycemics	Hypoglycemia	Diabetes complications
			Warfarin	Hemorrhage	Pulmonary embolism/MI/stroke
2D6	None	Bupropion Fluoxetine Fluvoxamine Paroxetine Quinidine	Aripiprazole	EPS/akathisia/dystonia	Psychosis
			Duloxetine	Increased blood pressure	Depression
			Mirtazapine	Somnolence	Depression/insomnia
			Iloperidone	Tachycardia/ hypotension/stiffness	Psychosis
			Tricyclics	Seizures/arrhythmia/anti-cholinergic	Depression
			Venlafaxine	Increased blood pressure	Depression
			Beta blockers	Hypotension	Hypertension
			Codeine/tramadol/hydrocodone	Less/no analgesia	Somnolence
3A4	Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Ginkgo biloba St. John's Wort	Nefazodone Grapefruit juice Protease inhibitors Ketoconazole Clarithromycin	Alprazolam	Sedation/intoxication	Panic/anxiety
			Aripiprazole	EPS/akathisia/dystonia	Psychosis
			Buspirone	Nausea/vomiting/dizziness/sedation	Anxiety
			Carbamazepine	Sedation/arrhythmia	Seizures
			Diazepam	Sedation/intoxication	Anxiety
			Quetiapine	Sedation	Psychosis
			Methadone	Sedation	Opiate withdrawal
			Oral contraceptives	GI upset	Pregnancy
			Calcium channel blockers	Hypotension	Hypertension
			Statins (not pravastatin)	Rhabdomyolosis	Hyperlipidemia

Drug Interactions in Psychiatry: A Practical Review

Continued from Page 2

the victim drug is broken down more rapidly, leading to lower levels. But since it takes a while for all this extra enzyme synthesis to occur, induction, unlike inhibition, does not happen immediately, but takes place over a one to three week period.

Now that you know the basics, how can you most efficiently apply them to your practice? Here are some tricks.

- Identify the 10 drugs that you most commonly prescribe, and memorize the major drug interactions for each one.
- Antidepressants, antipsychotics, antibiotics, antiretroviral, and older anticonvulsants have a high likelihood of significant drug interactions—so be particularly vigilant if your patient is taking any of these.
- Recognize the drugs with narrow therapeutic windows, ie, when the toxic dose is not much higher than the therapeutic dose. Commonly used narrow therapeutic window drugs include lithium, carbamazepine (Tegretol), warfarin (Coumadin), digoxin, phenytoin (Dilantin), and phenobarbital (Luminal).
- Recognize drugs that have serious side effects and outcomes if blood levels are significantly decreased or increased (eg, oral contraceptives, lamotrigine (Lamictal), clozapine, TCAs, warfarin).
- Drugs with long half-lives (eg, diazepam (Valium), aripiprazole (Abilify)) can be particularly troublesome when involved in drug interactions, because metabolic inhibitors can make them ultra long lasting.

Continued on Page 5

Q&A With the Expert

This Month's Expert

Drug-Drug interactions

Neil Sandson, MD

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Dr. Sandson has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

TCPR: Dr. Sandson, it seems that drug-drug interactions (DDI) were in our profession's consciousness more in the past than they are now. Is this because we have less to worry about than we used to?

Dr. Sandson: I think that there is a false sense of security, partly because with the increasing sophistication of some of the drug interaction computer programs, people have decided that that the computer is going to figure out for them if there are any interactions. But most of these programs are overly sensitive but not really specific, so users end up with alert fatigue and may not pay as much attention as they should to a potential interaction.

TCPR: What are some of the major interactions among psychiatric drugs that we should be aware of?

Dr. Sandson: Certainly among the antipsychotics, mood stabilizers, and antidepressants, there is plenty to be concerned about.

TCPR: Are there any particular antipsychotics that we need to worry about?

Dr. Sandson: The most pervasive issue to worry about is smoking. Smoking is a potent inducer of P450 1A2 [sometimes called the CYP1A2 enzyme]. This means smoking has the capability to cut drug levels of almost every typical antipsychotic, as well as the atypicals olanzapine (Zyprexa) and clozapine (Clozaril), roughly in half.

TCPR: Quite a lot of schizophrenic patients smoke. So how should we deal with this?

Dr. Sandson: I don't think that this represents any absolute or relative contraindication to using any of these drugs. It is just something that the clinician should be aware of in terms of appropriate prescribing. A typical scenario might be when a two-pack-a-day smoker who is on clozapine gets admitted—not because of treatment noncompliance, but for some other reason. With the cessation of smoking, enzymes in the body return to their lower baseline quantitative level, which produces a net decrease in metabolic activity vis-à-vis this drug, and then the blood level can rise quite rapidly. This could lead to side effects or something more striking, like a seizure.

TCPR: Conversely, I assume when patients start smoking, their serum levels decrease.

Dr. Sandson: Yes, and that is more insidious and easy to miss. Let's say you have someone in the nonsmoking hospital environment, and you have him or her pretty well treated with olanzapine 20 mg a day, for example. He or she makes no bones about resuming a two-pack-a-day habit the nanosecond after discharge. At that point, a predictable problem is going to arise, when a few days after discharge his or her antipsychotic blood level is cut in half. And that is something that we as clinicians really need to be mindful of and anticipate. We need to ask people: Are you going to resume smoking? Are you interested in help quitting?

TCPR: What should we do about those patients?

Dr. Sandson: If I really believe that the current dosage is appropriate and that a significant cut in the antipsychotic blood level would be deleterious to the patient, I would actually increase the dosage as he or she walks out the door. Just give an extra 10 mg to grow on—he or she might be a little groggier the first two or three days, but it will pass.

TCPR: Does it matter how much a person smokes?

Dr. Sandson: I believe it is a dose-dependent phenomenon, although we don't have any firm means of quantifying this.

TCPR: Are there any other clinically relevant DDIs that come up with antipsychotics?

Dr. Sandson: When you are coadministering potent enzymatic inhibitors, such as fluoxetine (Prozac) or paroxetine (Paxil), you can get new side effects, like EPS and hyperprolactinemia, due to increases in antipsychotic blood levels. Even ethinyl estradiol, often found in birth control pills, can produce increases in clozapine levels. Levels of antipsychotics can be reduced by drugs that induce enzymes that catalyze their metabolism, such as anticonvulsants like phenytoin (Dilantin), carbamazepine (Tegretol), or phenobarbital (Luminal); or antituberculosis drugs like rifampin (Rifadin).

TCPR: What about drug interactions involving mood stabilizers?

Dr. Sandson: Carbamazepine is one of our most frequently used inducers. Its presence in patients' regimens can lead to substantially lower blood levels of many drugs. Lamotrigine (Lamictal) is a little dicey in terms what will raise or lower blood levels; in particular, valproic acid (Depakote) can double lamotrigine levels. While ethinyl estradiol can increase the effects of many antipsychotics, it acts as an inducer of lamotrigine's metabolism and thus decreases levels of lamotrigine, as do phenytoin and phenobarbital.

TCPR: What kind of drug interactions occur with lithium?

Dr. Sandson: Our most common problem with lithium involves caffeine, which has a very significant influence on lithium levels. With an increase of maybe two more cups of coffee than is usual, you can drop lithium levels by about half. If a patient has his or her level drawn before the morning coffee, it may not be reflective of the rest of the day. Likewise, if you are administering the lithium based upon a period of high caffeine consumption and then your patient decides to go caffeine free, this could produce lithium toxicity.

TCPR: Anything else to worry about specifically with lithium?

Dr. Sandson: Most diuretics can potentially derange lithium levels. The thiazide diuretics will increase it by 25% to 40% on average, while

osmotic diuretics like the xanthenes drop lithium levels. Associated with diuretics are the drugs that affect angiotensin and aldosterone balance—like ACE inhibitors and angiotensin receptor blockers (ARBs)—which also increase lithium levels by about 25% to 40% on average.

TCPR: Another big one with lithium is nonsteroidal anti-inflammatories, right?

Dr. Sandson: The nonsteroidals, with the exceptions of aspirin and sulindac (Clinoril), tend to increase lithium levels to a variable degree, anywhere from 20% to 200%, and one can't reliably predict the magnitude of this interaction. Occasional use is no big deal, but if your patient is taking an NSAID on a standing basis, I think you should prospectively decrease the lithium level by a third, and then recheck that lithium level a week after the nonsteroidal has been started.

TCPR: Are there concerns with psychostimulants like methylphenidate or the stimulant-like drugs such as modafinil (Provigil) and armodafinil (Nuvigil)?

Dr. Sandson: Stimulants are generally more often victims—their levels are altered by other drugs—than perpetrators. Stimulant blood levels can be raised by any of the potent CYP2D6 inhibitors, such as fluoxetine, paroxetine, or bupropion. However, these drugs have high therapeutic indices, so this is often not a compelling clinical concern.

TCPR: I understand that Provigil and Nuvigil can induce the metabolism of the phosphodiesterase drugs for erectile dysfunction, like Viagra, Levitra, and Cialis.

Dr. Sandson: Theoretically, this could be a meaningful interaction, since the PDE inhibitors are metabolized by the CYP3A4 enzyme. However, I have yet to uncover, despite having looked for it, any case reports that demonstrate 3A4 inducers depriving phosphodiesterase inhibitors of their efficacy. What I can tell you conversely is that there is a literature about various CYP3A4 inhibitors, such as ritonavir (Norvir) and grapefruit juice, greatly increasing phosphodiesterase inhibitor levels, but apparently this is well-tolerated and although it is demonstrable, it does not seem to be something that is clinically significant.

TCPR: All these interactions are obviously tough to keep track of. In which patients should we be most vigilant of DDIs?

Dr. Sandson: I think we are moving into the very important domain of clinical wisdom at this point. It is not enough to know that a DDI is possible or even actual, but it all needs to be taken in the context of: how pharmacodynamically hardy is my patient? For example, what is the therapeutic index of the victim of the drug interaction? If I have a young, very healthy patient and I have a bunch of drugs, none of which has a particularly low therapeutic index, there might not even be a particular need to evaluate this list with great rigor, because the worst case scenario is not very bad at all. The story can be very different with people who are more medically compromised, or who are taking drugs that can have much more dire effects or for whom the stakes are higher if there is a lack of efficacy. So the lens through which one evaluates the DDI profile for each patient is going to differ based upon the characteristics of each and every patient.

TCPR: Is there anything we should be aware of in terms of prodrugs?

Dr. Sandson: The analgesic prodrugs like tramadol, codeine, and hydrocodone are particularly important. These drugs rely upon conversion via the enzyme 2D6 into active analgesic products. So any enzymatic inhibitors will thwart that and make these drugs less effective. These enzymatic inhibitors include fluoxetine, paroxetine, and bupropion. On the other hand, it has been found that if someone is a nonresponder to the prodrug blood thinner clopidogrel (Plavix), co-administering something like rifampin or St. John's Wort can change him or her into a responder by virtue of the CYP3A4 inductive capabilities of these drugs.

TCPR: Very interesting. Any final words of wisdom on drug interactions?

Dr. Sandson: The best DDI stories are not the ones where someone gets into trouble and after the fact you retrospectively evaluate how and why it happened. The best stories, albeit far less dramatic, are the ones where you anticipate the problem, prevent it, and nothing happens. It doesn't have as much eye-appeal, but certainly that is a victory for the physician, and most importantly, for the patient.

TCPR: Thank you, Dr. Sandson.

Drug Interactions in Psychiatry: A Practical Review

Continued from Page 3

- Be cautious with any new or rarely prescribed drugs, simply because neither you nor anybody else has had much experience with them, and unreported drug interactions can appear.
- The risk of drug interactions increase as the number of drugs increases. Setting a threshold to check for interactions is helpful (eg, any patient on three or more drugs).

Another important concern with drug interactions is timing. Inhibition happens quickly. It can occur with the first dose of a medication and it can subside quickly. How long it takes to subside depends on the inhibitor's half-life—generally, the inhibition will stop after five half-lives. For induction to occur, the body has to synthesize more CYP450 enzymes, and this can take up to four weeks. This accounts for the delayed "auto-induction" of carbamazepine. Conversely, for induction to subside, these extra enzymes need to be broken down. That process can take weeks to occur.

As a general rule of thumb, any drug prescribed with an inhibitor should be started at half the usual dose and titrated more slowly. Conversely, a drug prescribed with its inducer may need to be dosed higher after the few weeks it takes for induction to occur.

Useful References for Drug Interactions

The following programs allow you to input a group of drugs to check for interactions:

- **Free:**
  - Medscape (www.medscape.com/druginfo/druginterchecker)
  - Epocrates (www.epocrates.com)
  - www.drugs.com
- **Not free:**
  - iFacts (http://bit.ly/gvqocW), $59.95 one year subscription.
  - Lexi-Interact (http://bit.ly/fugKmk), $75 one year subscription

Free detailed table of substrates, inhibitors, and inducers: www.healthanddna.com/Druglist.pdf

Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

SCHIZOPHRENIA

Atypicals No Better Than Typicals in Depression with Schizophrenia

Second generation antipsychotics have developed a reputation for being more effective for treating a number of the symptoms of schizophrenia than their first generation counterparts, even if research doesn't always back up this claim. (For example, see *TCPR* November 2009 or Lieberman JA et al, *N Engl J Med* 2005;353(12):1209–1223.) Furthermore, American Psychiatric Association Clinical Practice Guidelines specifically recommend atypical over first generation agents to treat depression in schizophrenia (American Psychiatry Association. Practice Guidelines for Treatment of Patients with Schizophrenia, Second Edition. *Am J Psychiatry* 2004:161(suppl):1–55).

CATIE, or Clinical Antipsychotic Trials of Intervention Effectiveness, was the largest set of trials ever to compare the major second generation antipsychotics. The main results of Phase 1 were released in 2005 (*New Engl J Med* 2005;353(12):1209–1223), and since then, numerous studies have been done using that data (including this one). For a review of CATIE, see *TCPR,* March 2006.

Using data from the CATIE trial, researchers followed 1,460 patients with schizophrenia who were assigned treatment with the first generation antipsychotic perphenazine (Trilafon) (n=256) or one of four second generation antipsychotics: olanzapine (Zyprexa) (n=328), quetiapine (Seroquel) (n=328), risperidone (Risperdal) (n=332), or ziprasidone (Geodon) (n=182). Patients were assessed for depression using the Calgary Depression Scale for Schizophrenia (CDSS). Average medication dosages were as follows: Zyprexa—20.1 mg; Seroquel—543.4 mg; Risperdal—3.9 mg; Trilafon—20.8 mg; and Geodon—112.8 mg.

Patients in each medication group were followed for up to 18 months; median treatment times were as follows: Zyprexa—9.2 months; Seroquel—4.6 months; Risperdal—4.8 months; Trilafon—5.6 months; Geodon—3.5 months.

Depression scores improved for all medication groups, and there were no differences among the first and second generation antipsychotics. Among the second generation antipsychotics, however, there was a small but statistically significant greater improvement in depression scores for the group taking Seroquel when compared to the group taking Risperdal, but only among a subset of patients who met criteria for major depressive episode (only about 9 patients in each group) (Addington DE et al, *J Clin Psychiatry* 2010; Sept 21, online ahead of print).

TCPR's Take: *TCPR* has disputed the purported advantage of Zyprexa for core psychotic symptoms in the CATIE study because the drug was dosed more robustly than its competing agents. In this analysis, however, the fact that high-dose Zyprexa (as well as the other atypicals) yielded no benefit over Trilafon for depression is an important finding. This may be specific to Trilafon, which is a medium potency agent that is less likely than other first generation agents to cause symptoms that may appear to be depression, such as parkinsonism.

PATIENT PREFERENCE

Should We Give Patients the Treatment They Request?

Since antidepressants and psychotherapy are about equally effective for mild to moderate depression, how do we decide which to use for a given patient? Common sense would dictate that we simply ask patients which they would prefer. Presumably, if a patient has faith in one versus the other treatment, the placebo effect will augment whatever specific effect the treatment may have. But has research borne out this assumption?

As it turns out, there has been little research on this issue, and its quality has been mixed (Swift JK et al, *J Clin Psychol* 2009;65(4):368–381). A recent trial used an interesting methodology, both randomly assigning some patients to their preferred or non-preferred treatment, and also allowing some participants to select their treatment.

A total of 145 mildly to moderately depressed patients were randomly assigned to one of three groups: 1) 10 weeks of sertraline (Zoloft) 50 mg with possible dose escalation to 200 mg; 2) 10 sessions of group cognitive behavioral treatment (CBT); or 3) patient choice of either Zoloft or CBT. But before they were randomized, all patients were asked whether they preferred to receive a drug or psychotherapy for their depression.

The researchers then compared HAM-D scores and remission rates of patients who wanted or did not want the treatment to which they were assigned. And here's where things get interesting. In the Zoloft arm, the remission rate (RR) of those preferring a drug was 46%; the RR of those preferring therapy was 43%. In the CBT group, the RR of those preferring CBT was 43.9%; the RR of those preferring Zoloft was 0%. Similar results were seen on HAM-D scores. Clearly, patients who did not prefer psychotherapy had poor outcomes when assigned to receive CBT (Mergl R et al, *Psychother Psychosom* 2011;80(1):39–47).

TCPR's Take: The results only partially confirm the common sense view that when all other factors are equal, patients will do better when offered the treatment they prefer. Just about all patients improved equivalently in this trial—the glaring exception being those who wanted meds but were assigned to therapy. On the other hand, those

Continued on Page 8

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by January 31, 2012. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password, please email CME@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. Which of the following is NOT a juncture at which drugs might interact with each other in a pharmacokinetic interaction (Learning Objective #1)?
   - [ ] a. absorption
   - [ ] b. distribution
   - [ ] c. respiration
   - [ ] d. excretion

2. Pharmacodynamic interactions operate at the level of neurotransmitters and mechanisms of action (LO #1).
   - [ ] a. True
   - [ ] b. False

3. Which is a potential symptom of a drug interaction between fluvoxamine (Luvox) and asenapine (Saphris) (LO #2)?
   - [ ] a. hypoglycemia
   - [ ] b. GI upset
   - [ ] c. insomnia/EPS
   - [ ] d. rhabdomylosis

4. According to Dr. Neil Sandson, caffeine can decrease lithium levels by about half (LO #3).
   - [ ] a. True
   - [ ] b. False

5. In the Mergl et al study, the remission rate of patients in the CBT arm who had expressed a preference for treatment with Zoloft was what percent (LO #4)?
   - [ ] a. 0%
   - [ ] b. 33%
   - [ ] c. 43.9%
   - [ ] d. 56%

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

Your evaluation of this CME/CE activity (ie, this issue) will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives? L.O.#1: [ ] Yes [ ] No L.O.#2: [ ] Yes [ ] No L.O.#3: [ ] Yes [ ] No L.O.#4: [ ] Yes [ ] No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity? [ ] 5 [ ] 4 [ ] 3 [ ] 2 [ ] 1
3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice performance in a manner that improves your patient care? Please explain. [ ] Yes [ ] No

4. Did you perceive any evidence of bias for or against any commercial products? Please explain. [ ] Yes [ ] No

5. How long did it take you to complete this CME/CE activity? ___ hour(s) ___ minutes
6. **Important for our planning:** Please state one or two topics that you would like to see addressed in future issues.

Continued from Page 6

wanting therapy did just as well whether assigned to therapy or meds—which is something of a surprise. A potential explanation is that, according to the authors, patients were provided with "extensive education" about Zoloft after they had stated their treatment preference. This may have influenced some patients who felt negatively about Zoloft to feel more positively about the drug—which could have inflated the apparent Zoloft efficacy. Overall, the study's results suggest that we should provide treatment in accordance with our patient's preferences when feasible—though it may be especially important to respect the wishes of those patients who prefer medication treatment.

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