

# 2006 Guide to Psychiatric Drug Interactions

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## ABSTRACT

*Drug-drug interactions (DDIs) are a concern for the prescriber because they have the potential for causing untoward outcomes for everyone involved: morbidity and even mortality for the patient, liability for the prescriber, and increased costs for the healthcare system. The risk of unintended and untoward DDIs is increasing in concert with both the increasing number of pharmaceuticals available and the number of patients on multiple medications. Based on the 2004 Health and Human Services report, 7% of Americans >18 years of age and >20% of Americans >65 years of age had taken  $\geq 5$  prescription medications in the week preceding the survey. Additional studies have found that patients on psychiatric medications, such as antidepressants, are on more medications than patients not on psychiatric medications. It is important for prescribers to appreciate that medications interact not on the basis of their therapeutic use but on the basis of their pharmacodynamics and pharmacokinetics. For these reasons, the prescriber of psychiatric medications must consider all of the medications the patient is taking. Similar to the 2004 version, this educational review emphasizes the role of pharmacologic principles to guide the safe and effective use of multiple medications when such use is necessary. The review focuses on neuropsychiatric medications but also covers all other drugs to the extent that they interact with psychiatric medications. This review also presents tables outlining major pharmacodynamic and pharmacokinetic mechanisms mediating DDIs relevant to the patient on psychiatric medications.*

**Needs Assessment:** Multiple medication use is a fact of every day clinical practice. While it is often necessary to use several medications in order to achieve optimal treatment of the patient, it poses the risk of untoward drug-drug interactions. The outcome of such interactions can range from sudden catastrophic outcomes to reduced efficacy and tolerability problems. This article will aid the practitioner in avoiding unintended drug-drug interactions.

### Learning Objectives:

- Define what is a drug-drug interaction (DDI).
- Give examples of pharmacodynamic and pharmacokinetic DDIs.
- Use the tables provided in the article to avoid untoward DDIs.
- List the five major reasons why multiple medications are used together to treat patients.

**Target Audience:** Primary care physicians and psychiatrists.

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## INTRODUCTION

*Doctors pour drugs of which they know little, to cure diseases of which they know less, into patients of whom they know nothing.*<sup>1</sup>  
— Voltaire

*The true polypharmacy is the skillful combination of remedies.*<sup>2</sup>  
— Sir William Osler

*A physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.*<sup>3</sup>  
— Sir William Osler

The above quotes by Voltaire<sup>1</sup> and Osler<sup>2</sup> illustrate two sides of the same coin. That is, the advantages and the disadvantages of polypharmacy and the need for knowledge and skill to guide the clinician when using more than one drug in combination. The authors hope that this educational review will aid the reader in acquiring some of the needed knowledge and skill to safely and effectively prescribe multiple medications to a patient when that is truly needed. Still, the basic approach advocated by the authors is to use the simplest drug regimen whenever possible and to always review a patient's regimen to see if any current medication can be stopped when a new drug is being added. A common mistake is simply adding drugs without stopping others. For this reason, it is critical to always have a goal for every drug that is added. If the drug does not meet that goal, then either its dose should be adjusted or the drug should be stopped. One way to reduce unnecessary polypharmacy is declaring therapeutic failure and stopping medications which have not produced the desired therapeutic response within the expected timeframe.

## WHAT IS MEANT BY A DRUG-DRUG INTERACTION?

A drug-drug interaction (DDI) occurs when the presence of a co-prescribed drug (the perpetrator) alters the nature, magnitude, or duration of the effect of a given dose of another drug (the victim).

“Altered nature” means that the effect produced when the two drugs are used together is qualitatively different than would be expected when either drug is used alone. An example is serotonin syndrome, which consists of marked autonomic instability and can be fatal. This syndrome can occur when a serotonin uptake pump inhibitor is used in combination with a monoamine oxidase inhibitor (MAOI).<sup>3</sup>

“Altered magnitude,” on the other hand, means that the nature of the effect is the same as can be reasonably expected from the victim drug alone but is either more than or less than what would normally be expected for the specific dose ingested.

“Altered duration” means that the nature of the effect is reasonably the same as can be expected from the victim drug alone, but the effect is either shorter or longer lived than would normally be expected for the dose given.

## HOW DO DRUG-DRUG INTERACTIONS PRESENT AND HOW IMPORTANT ARE THEY?

Given this definition, it is easy to understand why DDIs can mimic virtually any clinical presentation imaginable from catastrophic to the every day problems seen in practice. That is why DDIs occur but may not be seen by the prescriber. What the prescriber may not “see” is the connection between the combined effects that drugs are causing and the clinical outcome he/she is observing. DDIs can present in all of the following ways:

1. A multitude of different types of serious adverse events (SAEs), such as sudden death,<sup>4-6</sup> seizures,<sup>7</sup> cardiac rhythm disturbances,<sup>8,9</sup> serotonin syndrome,<sup>10</sup> malignant hypertension,<sup>11</sup> neuroleptic malignant syndrome,<sup>12</sup> and delirium<sup>13,14</sup>
2. Poor tolerability (ie, patient is “sensitive” to adverse drug effect)<sup>8,9,15-19</sup>
3. Lack of efficacy (ie, patient is “resistant” to beneficial drug effect)<sup>20</sup>
4. Symptoms that mimic or lead to a misdiagnosis of a new disease<sup>21-23</sup>
5. The apparent worsening of the disease being treated<sup>15-17</sup>
6. Withdrawal symptoms or drug-seeking behavior on the part of the patient<sup>24</sup>

Preskorn has written a series of real-life case reports illustrating the myriad ways that DDIs can present and can be misdiagnosed leading to untoward outcomes for the patient and the prescriber, to aid prescribers in recognizing DDIs when they occur and to understand their clinical significance by giving them case-based examples. The interested reader can access those case discussions for free at [www.preskorn.com](http://www.preskorn.com) under the section, “Columns, Case Studies.”<sup>25</sup>

Some have wondered about the clinical relevance of DDIs from a population as opposed to a specific patient perspective (ie, what percent of a population experiences a clinically significant DDI). An extensive discussion of this issue is beyond the scope of this article but a few comments are warranted:

The first comment involves an estimate of the percentage of the population at risk for a potential DDI. Pharmacoepidemiology surveys done in Denmark,<sup>26-28</sup> England,<sup>29,30</sup> Sweden,<sup>31</sup> and the United States have all found multiple medication use to be extensive. Most patients were found to be on a unique combination of medications, meaning that no other person in the population studied was on exactly the same combination of medications. The populations studied in these surveys numbered in the thousands. Thus, a sizable percentage of the population, at least in industrial countries, is at risk for a DDI by virtue of being on multiple medications and, more importantly, unique combinations of medications.

The second is the issue of what constitutes clinical relevance, which has been discussed at length.<sup>32,33</sup> In essence, some might consider only catastrophic outcomes to be clinically significant. The authors take the position that any clinically significant change in the patient's status due to a DDI makes that DDI clinically significant and any of the outcomes listed above from SAEs to withdrawal symptoms can be clinically significant. In terms of SAEs, in their pharmacoepidemiology study, Ray and colleagues<sup>34</sup> found that the mortality rate in patients on erythromycin was five times higher than matched controls on comparable antibiotics which were not substantial cytochrome P450 (CYP) 3A inhibitors. Another population study, by de Leon and colleagues,<sup>19</sup> took poor tolerability leading to the discontinuation of the victim drug as the clinically significant outcome. The study found that the co-prescription of risperidone and a substantial CYP 2D6 inhibitor, such as fluoxetine, produced a >3-fold increase in the odds ratio for discontinuation of risperidone due to the development of acute extrapyramidal side effects (EPS) compared to individuals on a comparable dose of risperidone but not on a substantial CYP 2D6 inhibitor.

Of course, a DDI which causes noncompliance with prescribed antipsychotic treatment in a patient with schizophrenia can lead to a psychotic relapse with all of its associated potential untoward outcomes and yet the DDI may be missed and the noncompliance simply blamed on the patient. That is why not seeing is not the equivalent of not occurring. The reader who is interested in more about this topic is referred to the following references which address the topic of the clinical relevance of DDIs from a population perspective in greater detail.<sup>32,33</sup>

## GOAL OF THIS EDUCATIONAL REVIEW

The goal of this educational review is to provide a quick reference for prescribers about some of the major psychiatric DDIs. In doing so, it presents general concepts that can aid prescribers in avoiding untoward DDIs when possible, and quickly recognizing them when they occur. The latter is important because the rapid recognition that an untoward clinical outcome is due to an adverse DDI can permit the rapid implementation of corrective steps to minimize the consequences. This educational review is not intended to be comprehensive or authoritative. Given the speed with which new drugs are entering the market and new discoveries about the mechanisms underlying DDIs are being made, the authors recognize that this article, like all printed material on this topic, will quickly become dated. The authors have addressed some of these limitations by providing the reader with a list of Web sites that are more comprehensive and continuously updated (Appendix). This article provides an introduction to the topic and serves as a gateway to ready sources of additional information via the Internet.

Both authors maintain Web sites relevant to DDIs. Dr. Flockhart's Web site<sup>35</sup> summarizes data on CYP enzymes and the drugs they metabolize and outlines which drugs inhibit or induce CYP enzymes. This information can be used to predict and avoid DDIs mediated by this mechanism. Dr. Preskorn's Web site<sup>25</sup> provides content on topics relevant to the safe and effective use of psychiatric medications. For example, under "Columns, Case Studies", real-life examples of how DDIs present clinically and the mechanisms responsible for the DDI are presented.<sup>25</sup> The authors will refer to these and other Web sites as readily available resources for the reader who wants a more extended discussion of a topic or for those who want to check for updates even long after this article has been published.

Beyond the inevitability of all print material to become dated, this article has several other limitations, starting with the one imposed by its title: Drugs do not interact on the basis of their therapeutic class (eg, "psychiatric" vs "cardiac" medications) but instead on the basis of their pharmacodynamics (ie, their action on the body) and their pharmacokinetics (ie, the actions of the body on them, including their absorption from the site of administration, their distribution in the body, their metabolism, and their elimination).<sup>36</sup> For this reason, the authors acknowledge the limitations inherent in focusing on therapeutic class—even one as broad as psychiatric or neuropsychiatric medications. In fact, the authors will reclassify the drugs principally covered in this article into other functional classes based on their pharmacodynamics and pharmacokinetics.

ics, such as CYP enzyme substrates, inducers, and inhibitors. The reason for taking this approach is that those are the mechanisms that underlie clinically significant DDIs. For this same reason, the authors will also address the effects of psychiatric on nonpsychiatric medications and vice versa, where appropriate.

With these caveats, this review will focus on neuropsychiatric medications. The article will review the scope of the problem and discuss strategies and approaches to avoiding untoward and unintended DDIs. Summary figures embedded in the text and tables at the end of the article will highlight major DDIs involving psychiatric medications.

## CHANGES SINCE 2004

Our original article was published in early 2004,<sup>37</sup> which means it was written in 2003. Since 2003, 51 new drugs have entered the US market (Table 1). That translates into 17 new drugs a year or a new drug every 3 weeks. While 51 new drugs entered the US market since 2003, only four were formally classified as psychiatric medications: acamprosate (Campral) for alcohol dependence, duloxetine (Cymbalta) for major depression, eszopiclone (Lunesta) for insomnia, and ramelteon (Rozerem) for sleep-onset insomnia. This educational review will be updated for all 51 drugs in keeping with the principles outlined above, but those classified as psychiatric medications will receive special attention in accordance with the title of this article.

Of these drugs, duloxetine is arguably the most important because it will likely have the greatest use by the most diverse groups of practitioners given its antidepressant indication. For that reason, Table 2 has been added to present the differential effects of available antidepressants on CYP enzymes.<sup>38</sup> As can be readily seen in Table 2, the newer antidepressants with the most effects on CYP enzymes are fluoxetine and fluvoxamine. These two antidepressants would likely not be approved today for this reason and should be used cautiously, if at all, in patients on >1 medication or patients who may go on >1 medication. In other words, their use should be severely curtailed because they pose a significant risk of being a perpetrator of a clinically significant DDI. Bupropion, nefazodone, and paroxetine do not affect as many CYP enzymes as fluoxetine and fluvoxamine but nevertheless at usual clinical doses produce substantial inhibition of one CYP enzyme: CYP 2D6 in the case of bupropion and paroxetine and CYP 3A3/4 in the case of nefazodone. Hence, the careful use of these antidepressants in combination with other drugs is also warranted and prudent. The reason for this admonition is that there are multiple antidepressants as seen

in Table 2 that do not substantially inhibit any CYP enzyme at their usual antidepressant dose: citalopram, escitalopram, mirtazapine, sertraline, and venlafaxine. This caveat is particularly true for fluoxetine, fluvoxamine, and paroxetine because their pharmacology beyond CYP enzyme inhibition is so similar to that of citalopram, escitalopram and sertraline. The practitioner can thus use this table to help decide which antidepressant he/she wants as their preferred antidepressant in their personal formulary as discussed below.

While duloxetine is the most important for the reasons outlined above, all of the following deserve special mention in terms of CYP enzyme-mediated DDIs:

- *Duloxetine* is a substrate of CYP 2D6 and CYP 1A2. Paroxetine, a known substantial CYP 2D6 inhibitor, increases the concentration of duloxetine by approximately 60%.<sup>39</sup> Similar effects should be expected with other potent CYP 2D6 inhibitors (fluoxetine, quinidine). Co-administration of duloxetine with fluvoxamine, a strong CYP 1A2 inhibitor, increases the maximal concentration ( $C_{max}$ ) of duloxetine 2.5-fold and the area under the curve (AUC) 5-fold.<sup>40</sup> For this reason, the combination of duloxetine and other CYP 1A2 inhibitors (eg, fluoroquinolones) should be avoided.<sup>40</sup> At a dose of 120 mg/day, duloxetine is a moderate inhibitor of CYP 2D6 and a mild inhibitor at a dose of 60 mg/day using the definition outlined in Table 2.<sup>41,42</sup> Duloxetine at 120 mg/day increases the  $C_{max}$  and AUC of desipramine, a drug almost exclusively metabolized by CYP 2D6, by 1.7- and 2.9-fold, respectively.<sup>41</sup> Duloxetine at 60 mg/day increases the  $C_{max}$  and AUC of metoprolol, another drug almost exclusively metabolized by CYP 2D6, by 1.0- and 1.8-fold, respectively.<sup>42</sup> These results provide another example of the usual dose-dependent nature of the inhibition of CYP enzyme function. Given these results, drugs that are principally metabolized by CYP 2D6 and have potentially severe dose-dependent adverse effects should be co-administered cautiously with duloxetine. Such drugs include: tricyclic antidepressants (TCAs), phenothiazines, and type 1C anti-arrhythmics: propafenone and flecainide.<sup>40</sup>
- *Ramelteon* is a substrate of CYP 1A2, CYP 3A4, and substantial 2C9. Fluvoxamine, a strong CYP 1A2 inhibitor, increases ramelteon AUC and  $C_{max}$  approximately 190-fold and 70-fold, respectively. Other CYP 1A2 inhibitors (eg, fluoroquinolones) would be expected to have similar effects.<sup>43</sup> Ketoconazole, a strong CYP 3A4 inhibitor, increases the  $AUC_{0-inf}$  and  $C_{max}$  of ramelteon by approximately 84% and 36%, respectively. Ramelteon should be administered

with caution in subjects taking other CYP 3A4 inhibitors (eg, itraconazole, erythromycin, clarithromycin, ritonavir).<sup>44</sup> Total and peak systemic exposure ( $AUC_{0-inf}$  and  $C_{max}$ ) of ramelteon increases by approximately 150% when administered with fluconazole, a CYP 2C9 inhibitor. Ramelteon should be administered with caution in subjects taking other CYP 2C9 inhibitors, such as fluconazole and fluvoxamine.<sup>44</sup> Administration of rifampin, a CYP 3A4 and CYP 2C9 inducer, results in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon (both AUC and  $C_{max}$ ).<sup>43</sup> For this reason, ramelteon efficacy may be reduced when used in combination with CYP 1A2, CYP 3A4, or CYP 2C9 inducers (eg, phenobarbital, carbamazepine, phenytoin).

- *Eszopiclone* is metabolized by CYP 3A4 and CYP 2E1. Co-administration of eszopiclone and ketoconazole, a substantial CYP 3A4 inhibitor, results in a 2.2-fold increase in exposure to eszopiclone.<sup>45</sup> The dose of eszopiclone should be reduced when it is administered with ketoconazole or other substantial CYP 3A4 inhibitors, such as itraconazole, clarithromycin, and ritonavir.<sup>46</sup> Racemic zopiclone exposure decreases 80% by concomitant use of rifampin, a substantial CYP 3A4 inducer. A similar effect would be expected with eszopiclone, potentially reducing its efficacy.<sup>45,46</sup>
- While atazanavir and fosamprenavir are not psychiatric medications, they deserve mention here because they are substantial CYP 3A inhibitors and, thus, can be the perpetrator of DDIs with a wide variety of psychiatric medications principally dependent on this CYP enzyme for their clearance.<sup>47,48</sup> For example, the concomitant use of atazanavir or fosamprenavir and drugs that are dependent on CYP 3A for clearance (eg, midazolam, triazolam, pimozide) is contraindicated.
- *Telithromycin* is another substantial CYP 3A inhibitor.<sup>49</sup> For this reason, it should also be used cautiously with other CYP 3A substrates (eg, midazolam, triazolam). Telithromycin may increase pimozide plasma levels by inhibition of CYP 3A4 pathways. In addition, telithromycin, like pimozide, can prolong the QTc interval. Hence, there is the potential for both a pharmacodynamic and pharmacokinetic DDI leading to the development of a fatal arrhythmia.

Returning to Table 1, a close examination reveals the forces that are at work in modern drug development and which have implications for the future of clinical psychopharmacology: Most of the drugs in that table are for relatively uncommon diseases but nevertheless diseases for which there is basic

knowledge about their pathogenesis or pathophysiology. In contrast to this situation, virtually all psychiatric illnesses are still understood almost exclusively at the syndromic level of diagnostic sophistication.<sup>50</sup> As information about the pathogenetic and pathophysiologic mechanism underlying different psychiatric illnesses becomes available, the reader can expect that the number of psychiatric medications entering the market place will explode. They will be better targeted to specific disease processes and will likely occur concomitant with the division of current syndromic diagnoses into multiple different diagnoses based on pathophysiology or pathogenesis. Nevertheless, this anticipated explosion of psychiatric medications will undoubtedly increase the frequency and complexity of polypharmacy and thus further heighten the potential for DDIs and the need for prescribers to be knowledgeable about this issue for years to come.

## POLYPHARMACY: THE REAL LANDSCAPE OF CLINICAL PRESCRIBING

The prescriber does not have to wait for the explosion of psychiatric medicines to feel somewhat overwhelmed. One such explosion already occurred following the introduction of fluoxetine in 1988.<sup>51</sup> While that explosion was a blessing in many ways, it nevertheless has posed serious challenges for practitioners trying to keep abreast of new developments. The prescriber has more therapeutic options, each with different pharmacodynamics and pharmacokinetics, to understand and weigh.

In addition, treatment over the last several decades has moved from a focus on time-limited therapy (ie, a few weeks) of an acute illness (eg, antibiotics for an acute infection) to preventive or maintenance therapy for chronic illnesses as diverse as major depressive disorder (MDD), schizophrenia, Alzheimer's disease, hypertension, human immunodeficiency virus infection, and atherosclerosis. For this reason, patients are much more likely to be on more than one medication at the same time.<sup>52-55</sup> In fact, they are likely to accumulate preventive therapy as they age. These therapies can often continue for many months or years, to perhaps the entire remaining life span of the individual once started. For this reason, the potential for DDIs increases over the life span of the individual.

As would be expected given the above, age is repeatedly found to be a risk factor for polypharmacy in pharmacoepidemiology studies as illustrated in Table 3.<sup>56-58</sup> However, some readers may be surprised to learn that being on a psychiatric medication is a greater risk factor for polypharmacy than is advanced age

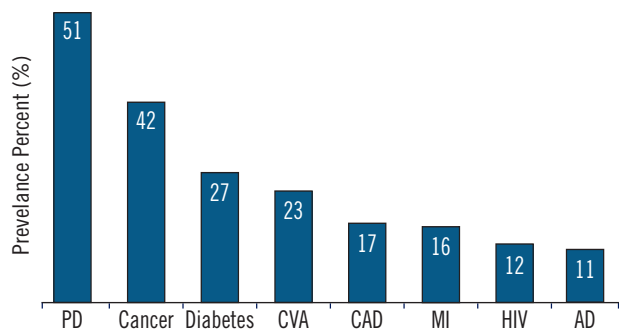
(Table 3). As is also seen in Table 3, the percentage of the different populations on a unique combination increases in direct relationship to the average number of drugs used to treat that specific population. Finally, one study found that the percentage of the population on  $\geq 8$  medications doubled as a function of the number of different prescribers the patient saw.<sup>56,57</sup> The fact that patients on antidepressants, for example, are on more multiple medications than patients not on these medications holds true regardless of whether they are being seen by a psychiatrist or another type of healthcare provider (Table 4).<sup>59,60</sup>

There are undoubtedly numerous reasons why psychiatric medications, such as antidepressants, mark a population at risk for polypharmacy. First, psychiatric illnesses such as MDD have an increased frequency in patients with other medical illnesses (Figure 1).<sup>61-64</sup> Second, patients with one psychiatric illness are at increased risk for other psychiatric disorders.<sup>65</sup> Third, patients with depressive and anxiety disorders are high utilizers of healthcare services and thus may be treated symptomatically with other medications.<sup>63,66-71</sup> Regardless of the reason, the prescriber should be aware of this fact and take it into account when developing the treatment plan for their patient.

The use of multiple psychiatric medications has increased over the last 2 decades, probably reflecting both the increased availability of effective medications and the fact that they have a more focused or limited pharmacology. The latter leads to better tolerability but may also limit efficacy and, thus, require the use of more medications to optimize patient outcomes.

These factors may explain at least in part why the use of multiple psychiatric medications to treat patients is on

**FIGURE 1**  
**PREVALENCE OF DEPRESSION IN PATIENTS WITH DIFFERENT CHRONIC DISEASES<sup>61-64</sup>**



PD=Parkinson's disease; CVA=cardiovascular accident; CAD=coronary artery disease; MI=myocardial infarction; HIV=human immunodeficiency virus; AD=Alzheimer's disease.

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the rise. For example, there has been a 15-fold increase in percentage of patients on three or more psychiatric medications being seen at the Biological Psychiatry Branch of the National Institute of Mental Health from the early 1970s to the mid-1990s (Figure 2).<sup>72</sup>

For all of the above reasons, patients on psychiatric medications are at risk for DDIs, and these DDIs are likely to involve more than just two drugs. Thus, the problem may not just be the effect of drug A on drug B but this effect in the presence of drugs C, D, and E.

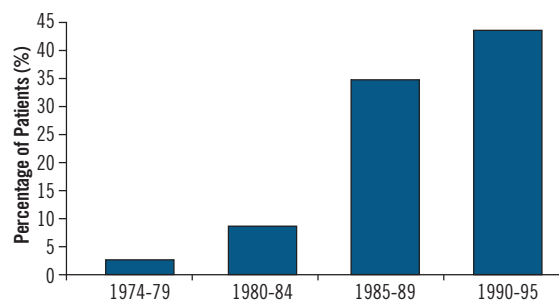
To underscore the complexity of such DDIs, consider the following questions, which help to illustrate the size of the problem:

1. In 2006, how many discrete chemical entities could a physician prescribe for his/her patient?
2. Given that number of drugs, how many different combinations of up to five drugs, could the physician prescribe for his/her patient?
3. The first new drug approved in 2006 could be prescribed in how many different combinations (up to 5 drugs), given the number of drugs already on the market when that new drug is introduced?
4. On average, how many new drugs have been introduced to the US market every year over the last 3 years?

The answers are:

1. >3,200 different drugs
2. 2.8 X 1,015
3. 4.4 trillion
4. 17 every 3 weeks (ie, 51 divided by 3 years or 156 weeks).

**FIGURE 2**  
**INCREASING USE OF POLYPHARMACY\* AT THE NIMH BIOLOGICAL PSYCHIATRY BRANCH BETWEEN 1974 AND 1996<sup>72</sup>**



\*  $\geq 3$  medications at discharge.

NIMH=National Institute of Mental Health.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 13, No 4. 2006.

## DRUG INTERACTIONS AND MEDICATION ERRORS

Given the above numbers, DDIs are, not surprisingly, a serious cause of concern for the US healthcare system. They are so numerous that the dictum to “do no harm” is seriously challenged. As illustrated by the answers above, this situation is in part due to the large number of new prescription drugs available to prescribers. For medical students who graduated from medical school in 2001, 115 new prescription drugs had been approved by the Food and Drug Administration during the time they were in medical school.<sup>73</sup> In contrast, students graduating in 1973 had to contend with only 57 new drugs being approved during their 4 years of medical school.<sup>73</sup> The number of drugs available over the counter (OTC) has also increased.

The potential number of DDIs has increased to the point where prescribers universally find it impossible to remember all conceivable interactions and are forced to rely on electronic media. To put their implications in perspective, consider that from 7,000 to as many as 98,000 deaths every year are caused by adverse drug events, mainly due to DDIs. That represents more deaths caused by DDIs than those caused by smoke inhalation or airplane accidents combined. While the US has generated elaborate, nationwide safety control systems to prevent deaths due to airplane accidents, nothing approaching such an effort has been done to prevent deaths due to DDIs.<sup>74</sup>

In much the same way as it is important to develop some understanding of why fires occur and the characteristics of fatal airplane accidents, the importance to the public health of a mechanistic understanding of adverse drug events, and of a system to prevent them, cannot be over-emphasized. DDIs not only cause serious and even fatal adverse events but they have also been a significant contributor to the withdrawal of a number of otherwise safe and effective medicines from the US market over the last decade, including: terfenadine, cisapride, astemizole, mibefradil, and, most recently, cerivastatin.<sup>75</sup> The financial impact of such withdrawals on the manufacturers of these drugs conservatively involves billions of dollars.<sup>76</sup>

In addition, the prescriber’s task is made even more difficult as a result of the growing number of significant interactions that result from co-medication with herbal nutritional supplements, a market on which the US public spends more than they do on prescription medicines.<sup>77</sup> Finally, the US population is aging and the

adverse events experienced by the elderly are markedly increased in those on  $\geq 4$  medications.<sup>78</sup>

The convergence of these multiple complicating influences makes clear that the simple medication history that all physicians are taught to take, consisting of the question “What medications do you take and do you have any allergies to drugs?” has not evolved to accommodate the complexity of these concerns. Therefore, the authors have proposed a more detailed series of questions using the acronym AVOID (Table 5). The authors will attempt herein to describe the principal mechanisms by which important DDIs with neuropsychiatric drugs occur, and to list those that are most likely to occur and result in clinically significant changes in drug activity.

## STRATEGIES TO MINIMIZE ADVERSE OUTCOMES FROM UNINTENDED DRUG-DRUG INTERACTIONS

### A Personal Formulary: Concept and Criteria

While all physicians are taught pharmacology in medical school, many, if not most, of the drugs that the average prescriber uses were not available during their training. For this reason, the value of a personal formulary in an era of polypharmacy and pervasive and potent marketing cannot be overemphasized. Rational prescribing in an era when so many drugs are available is close to impossible without it. Such a formulary should consist of the drugs that are used virtually every day in the clinician’s practice and that he/she is intimately familiar with. Inevitably, this list cannot be that large. The number of drugs in a personal formulary will vary, but a reasonable number is 10–15 drugs for a practicing psychiatrist, family practitioner, or internist.

The physician should truly be an expert on these medications that he or she commonly uses. That includes their generic and brand names, pharmacokinetics, pharmacodynamics, adverse effects, and potential DDIs. A high level of knowledge about a few drugs insulates the physician against trivial advertising and protects one’s patients from prescribing errors. The essential elements of knowledge that the physicians should know about each drug in their personal formulary is listed in Table 6.

It should not be easy for a drug to enter a personal formulary. Diligent study of the drugs in question, careful evaluation of the literature pertaining to them, and ongoing checks of new developments should be a routine habit

for the prescriber. If nothing else, these criteria allow the prescriber a means of focusing his or her attention within the sea of the medical literature. Thus, physicians become real experts in the use of a small number of drugs important to their practice.

In the 21st century, it is not enough to be an excellent diagnostician familiar with the use of laboratory and procedural testing; being expert in treatment is also required, and that requires an intimate knowledge not of all drugs available, but of 10–15 that a particular prescriber commonly uses. This foundation of knowledge can then serve as a basis for the evaluation of new drugs as they appear.

### **Generic Names**

At a minimum, a prescriber should be aware of the generic name of a medication on their personal formulary, without which it is impossible to search the medical literature on it or to recognize it on a board exam. As medicine becomes more international and the world becomes smaller, the physician must be aware that medications have different brand names in different countries, and frequently have multiple brand names (Table 7).<sup>79</sup> For example, there are 18 different brand names for fluoxetine in Italy.

The use of the generic name in prescriptions allows cheaper generic drugs to be used when they are available. Despite claims to the contrary, there are only a small number of examples where an approved generic is not an effective substitute for the brand name drug.

Lastly, persistent confusion over the similarity of drug names, either written or spoken, accounts for approximately 25% of all reports to the US Pharmacopeia Medication Errors Reporting Program, and the case for the use of both a generic name and brand name in legible handwriting on prescriptions is strong. For example, confusion has been reported between the antidepressant nefazodone (Serzone) and the antipsychotic quetiapine (Seroquel), both of which are available as 100 mg and 200 mg tablets. Also, the brand name of the antidepressant paroxetine (Paxil) has been confused with the brand name of the anti-platelet agent clopidogrel (Plavix).

To illustrate the above, a list of generic names of the most commonly used antidepressants in the US and their brand names is included in Table 8.<sup>80</sup> Although many have made the case that a switch to e-prescribing may obviate this problem, incorrect selection of a drug name from a computerized list has already been shown to be a significant problem; thus, there is one more argument making the case for routinely using both the generic and the brand names as a means of ensuring quality in prescribing.

### **Pharmacokinetics**

Prescribers should be aware of the routinely used doses and the serum half-life of the drugs they frequently use. In the case of psychiatric drugs, they should also be aware of its mechanism(s) of action and binding profile for relevant specific receptors (Tables 8–11).<sup>5,47,51-55,80</sup> This basic information can guide prescribing in a number of valuable ways, particularly by making prescribers aware of the potential pharmacodynamically mediated DDIs and their likely clinical outcomes for the patient.

### **The Therapeutic Alliance**

A therapeutic alliance is a group of people who communicate with each other about an individual patient's therapeutic plan and medications. Even the highest quality of prescribing cannot work if the patient is noncompliant, but patients, particularly those with brain diseases, often need help in maintaining adherence with what can be a demanding medication schedule. To this end, a therapeutic alliance involving the patient and the people around them is nearly always valuable. Family members should often be part of the therapeutic alliance, as well as the pharmacist, nurse practitioner, home health visitors, and friends (when appropriate). A system of prescribing, in which members of the therapeutic alliance are identified early in a patient's therapeutic plan and then involved in the follow-up, is as important as the valuable practice of routine checks by telephone or e-mail within a few days after a drug is prescribed.

### **Establishment of a Therapeutic Goal**

Any prescription should have a clear therapeutic goal. It might be reducing a serum low-density lipoprotein or blood pressure or relieving depression; regardless of the goal, a clear time expectation should be attached to it. For example, in the "Plan" section of a medical chart, an appropriate entry would be: "Reduction of depressive symptoms by 50% within 3–4 weeks." The setting of such goals is important because it allows the iterative optimization of therapy: If the goal is not achieved, then it is reasonable to have a conversation with the patient about compliance and side effects and to consider dose adjustment. The same applies to the treatment of psychiatric disorders other than depressive disorders, as well as nonpsychiatric medical illness. Therapeutic goals should be clearly delineated in charts and communicated to patients and the care providers that are involved with each patient.

## CONCEPTUAL FRAMEWORK FOR PRESCRIBING IN AN ERA OF POLYPHARMACY

### Principles of Pharmacology

As mentioned at the beginning of this article, a DDI occurs when the presence of a co-prescribed drug (the perpetrator) alters the nature, magnitude, or duration of the effect of a given dose of another drug (the victim). Given this definition, DDIs can obviously be therapeutic or adverse, intended or unintended, but they are always determined by the pharmacodynamics and pharmacokinetics of the co-prescribed drugs. Parenthetically, the prescriber wittingly or unwittingly is counting on a therapeutic DDI whenever they use one drug to treat an adverse effect or to boost the therapeutic benefit of another drug.<sup>81</sup> The focus of this article, however, is to minimize the risk of unintended and untoward DDIs and therefore will not consider therapeutic DDIs. Given the above definition of a DDI, the following two equations are essential to understanding and avoiding DDIs:

#### EQUATION 1

Effect =	affinity for and intrinsic activity at a site of action.	X drug level (absorption, distribution, metabolism, elimination [ADME]).	X biological variance (genetics, age, disease, environment [GADE]).
----------	----------------------------------------------------------	--------------------------------------------------------------------------	---------------------------------------------------------------------

#### EQUATION 2

$$\text{Drug Concentration} = \frac{\text{Dosing Rate}}{\text{Clearance}}$$

Equation 1 presents the three variables that determine the effect a drug will produce in a patient. First, the drug must work on a site of action (the first variable in Equation 1) which is capable of producing the effect observed. For all drugs, except anti-infectives, the site of action is a human regulatory protein such as a receptor, an enzyme, or an uptake pump. By binding to its target(s), the drug is capable of altering the functional status of the target(s) and thus altering human physiology. The ability of the drug to bind to the regulatory protein gives it its potential action (ie, its pharmacodynamics).

For the drug to express its potential action, it must reach the target to a sufficient degree to engage it to a physiologically relevant extent. That is the domain of the second variable in Equation 1. Drug concentration in relation to the drug's binding-affinity profile determines what site of

action the drug will bind to and to what degree. At low concentrations, the drug will bind to its most potent target. As the concentration increases, the drug will bind more substantially to that target until it is saturated. It will also begin binding to lower affinity targets when its concentration reaches a sufficiently high degree relative to its binding affinity for secondary targets.<sup>82,83</sup>

Equation 2 illustrates that drug concentration is a function of the dosing rate the patient is taking relative to their ability to clear the drug. This equation explains why clearance is as important as dose in determining the nature, the magnitude, and the duration of a drug's effect on the patient.

Clinical trials are, in essence, population pharmacokinetic studies in which the goal is to determine the usual dose needed for the usual participant (ie, usual clearance) enrolled in the clinical trial to achieve a concentration sufficient to engage the desired target sufficiently to produce the best balance between efficacy and safety/tolerability. Thus, the second variable in Equation 1 is the drug's pharmacokinetics (or drug movement), which has four phases summarized by the acronym **ADME**: **A**bsorption of the drug from the site of administration into the body, **D**istribution of the drug to the various compartments of the body (eg, plasma, termed the "central compartment," and tissues, or "deeper compartments" such as the brain), **M**etabolism or biotransformation into more polar substances, and finally, **E**limination from the body.<sup>36</sup>

The last variable in Equation 1 is the interindividual differences among patients, which can shift the dose-response curve making patients either more or less sensitive to the effect of the drug. These differences (ie, biological variance among patients) are summarized by the acronym **GADE**: **G**enetics, **A**ge, **D**isease, and **E**nvironment. The environment variable refers to the internal environment of the body, which includes other drugs or dietary substances the patient may be taking. These four variables modify the first two variables and, thus, explain how the magnitude, duration, or even the nature of the effect of the drug in a specific patient may differ from the usual effect produced by a given dose of the same drug. Thus, DDIs occur when one drug (the perpetrator) changes the effect of a given dose of another drug (the victim) by either interacting with it pharmacodynamically or pharmacokinetically (ie, the first and second variables in Equation 1). This concept is the essential principle underlying DDIs and the basis for the rest of this article.<sup>59</sup>

### Can Polypharmacy in Psychiatry Be Rational?

For polypharmacy to be rational, the prescriber in any area of medicine must be able to answer the following questions:

1. Why am I using more than one drug?
2. Do the drugs interact?
3. If so, what are the data that support the safety, tolerability, and efficacy of the combination?

Table 13 lists five major reasons why a prescriber may use more than one drug to treat a patient.<sup>59,81</sup> The first reason is the most obvious: The patient has more than one disease process and the prescriber must employ one or more agents for each disease. In this example, the prescriber is not planning a DDI, though one may occur because drugs interact on the basis of the mechanisms underlying their pharmacodynamics and pharmacokinetics rather than on the basis of their therapeutic indication. For this reason, the prescriber of psychiatric medications must be aware of and consider all of the medications the patient is taking.

The second reason listed in Table 12 is particularly relevant to psychiatry.<sup>59,81</sup> Conditions such as bipolar and schizoaffective disorder are complex symptom clusters that wax and wane over the course of the illness. Patients with these illnesses may need different medications for different phases of their illness. While mood stabilizers (eg, lithium) are usually the foundation for the treatment of a patient with bipolar disorder, the patient may at different phases of the illness need to have antidepressants, antipsychotics, or anxiolytics added and may even need treatment with >1 mood stabilizer. This situation is similar to that of epileptic patients. Many of these patients need to be on >1 anticonvulsant to achieve optimal control of their seizures.<sup>84,85</sup>

The remaining reasons listed in Table 12 are all based on planned therapeutic DDIs, whether or not the prescriber thinks in these terms.<sup>59,81</sup> When a second drug diminishes, amplifies, or speeds the onset of the effect of a first drug, that is, by definition, a DDI. When using a drug for these purposes, the ideal situation would be one in which the pathophysiology of the illness and the effects of each drug on that pathophysiology are all clearly understood. An example is Parkinson's disease, as outlined in Table 13.<sup>59,81</sup>

The problem in psychiatry is that the pathophysiology of psychiatric illnesses is not well understood and, thus, the effects of the drugs on that pathophysiology cannot be well understood. Nevertheless, Table 14 lists a series of features that can be used to rationally prescribe two or more psychiatric medications together to accomplish the last three goals listed in Table 12.<sup>25,59,81</sup>

## Beyond Psychiatric Drugs: the Total Therapeutic Regimen

The prescriber of psychiatric medications cannot simply focus on those medications but must examine all of the

medications the patient is taking, including OTC medications, illicit substances, herbal products, and even dietary substances. For example, ibuprofen, an OTC analgesic, can cause serious and even life-threatening elevations in lithium levels by affecting its rate of tubular re-absorption.<sup>86</sup> The duration of the effect of illicit substances can be prolonged by co-prescribed drugs, which inhibit the enzymes responsible for clearing the illicit substance. St. John's Wort is a substantial inducer of CYP 3A and can accelerate the clearance of a number of co-prescribed medications.<sup>87</sup> Smoking can induce the metabolism of drugs such as clozapine, which are normally cleared by smoking-inducible CYP 1A2.<sup>45</sup> Thus, the prescriber must take the whole patient into consideration when trying to understand and/or predict the effect of a treatment regimen involving more than one medication.

## Special Considerations for How DDIs Present in Psychiatry

The term "drug-drug interaction" frequently conjures images of a sudden catastrophic and even fatal outcome. While such an event can occur and is obviously important to prevent, DDIs can present as virtually anything, including the worsening of the illness being treated or the emergence of a new illness. For this reason, such "masked" DDIs can ironically lead to the use of more medications to treat the apparent worsening of the primary condition or to treat the apparent emergence of a new condition.

All drugs, except anti-infectives, are given to change human physiology.<sup>88</sup> Those changes can present in every way clinically imaginable. For this reason, the prescriber should keep in mind that the patient may not be doing well because of the medications he is receiving rather than despite the medications he is receiving.<sup>59</sup>

Understanding and identifying DDIs with psychiatric medications is perhaps more challenging than in any other area of medicine. The reason is the complexity of the organ they affect and the complexity of its output (Table 15).<sup>89</sup> The average human adult is composed of approximately 10–20 billion cells arranged in hierarchal and integrated systems. Seventy-five neurotransmitters have been identified in the human brain. That number may double in the next 10 years as a result of discoveries made possible by the human genome project. Every identified neurotransmitter has 2–17 receptor subtypes. Thus, the human brain may contain thousands of receptors, which are the primary targets of drug action. There are also different enzymes for the synthesis and degradation of these neurotransmitters, different uptake pumps, and storage mechanisms. All of these

regulatory proteins can be the target for drug action. Thus, current drugs may interact pharmacodynamically in ways that are neither understood nor predictable at the present time.<sup>59</sup> Their detection is dependent on the careful assessment at the time of a medication check by the prescriber.

As psychiatric drugs are more rationally developed to affect only the brain, their adverse effects will not be on peripheral systems but on the brain. The result of psychiatric DDIs can present as changes in mentation, reality testing, emotional control, interpersonal relationships, and memory function. The prescriber of psychiatric medications must be a good behavioral pharmacologist, as well as a good diagnostician, and must also keep in mind that changes in these outputs of the human brain may be because of the medications that the patient is receiving rather than in spite of them. This discussion further emphasizes the limitations of this article and of all information systems in clinical psychopharmacology. There is much more that needs to be known. In the interim, the goal of this article is to summarize what is known, to explain the limits of current knowledge, and to define good clinical practices as they relate to avoiding untoward DDIs.

## PROPER USE OF THERAPEUTIC DRUG MONITORING

Equation 1 illustrates that drug concentration determines what site(s) of action are engaged and to what degree, while Equation 2 illustrates that drug concentration is the dosing rate divided by the clearance. By rearranging Equation 2, it is clear that:

$$\text{Clearance} = \frac{\text{Dosing Rate}}{\text{Drug Concentration}}$$

If the prescriber is confident in the dosing rate (ie, noncompliance is not an issue), then measuring the drug concentration allows the prescriber to assess the patient's clearance to determine whether it is usual or unusually fast or slow. For example, if the clearance is faster or slower than usual, then the dosing rate must be changed proportionately to reach the usual drug concentration achieved on the usually effective dose; the usual site(s) of action is engaged to the usual degree associated with optimal response as determined by the registration trials that led to the marketing of the drug. Thus, the goal of therapeutic drug monitoring (TDM) is not to simply know whether the concentration is therapeutic but to know whether the patient's ability to clear the drug is usual or not. If not, the results of TDM can provide a rational basis for determining what sort of an adjustment in the dosing rate must be made to compensate for the patient's unusual clearance.

This issue is of critical importance when understanding and avoiding untoward effects mediated by the co-prescription of a drug capable of either inducing or inhibiting the enzymes responsible for the clearance of the victim drug. Induction can increase the clearance of the victim drug such that its levels fall below what is usually therapeutic, resulting in either loss of efficacy or withdrawal symptoms.<sup>90</sup> Inhibition can decrease the clearance of the victim drug such that its levels rise, causing consequences, which may range from an increase in the frequency and severity of dose-dependent adverse effects, such as EPS in the case of conventional antipsychotics to life-threatening toxicity in the case of tricyclic antidepressants (TCAs).

The logic underlying pharmacokinetic interactions mediated by the induction or inhibition of CYP enzymes is outlined in Figure 3.<sup>59,79</sup> This logic forms the basis for the section on CYP enzyme-mediated DDIs with psychiatric medications.

## Time Course of Interactions

Drugs have the potential to interact as long as they and/or their effects persist in the body. Thus, the potential for an interaction may persist for days to weeks and even months after one of the drugs has been discontinued.

This fact is illustrated in Figure 4 from a study examining the effect of fluoxetine on the metabolism of the CYP 2D6 model substrate desipramine.<sup>91</sup> In this study, genotypically normal metabolizers via CYP 2D6 (>95% of the population) were first treated with desipramine 50 mg/day for 7 days to achieve steady-state conditions. On day 8, fluoxetine 20 mg/day was added to their regimen. Without changing the dose of desipramine, its levels increased >4-fold over the next 3 weeks as fluoxetine and its active metabolite, norfluoxetine, accumulated, resulting in the inhibition of CYP 2D6. The inhibition of CYP 2D6 resulted in a reduction in the clearance of desipramine (Equation 2) and hence an increase in desipramine levels without a change in its dose.

**FIGURE 3**  
**HOW KNOWLEDGE OF CYP ENZYMES WILL SIMPLIFY UNDERSTANDING OF PHARMACOKINETIC INTERACTIONS<sup>59,79</sup>**



\* Could be inhibition or induction.

CYP=cytochrome P450.

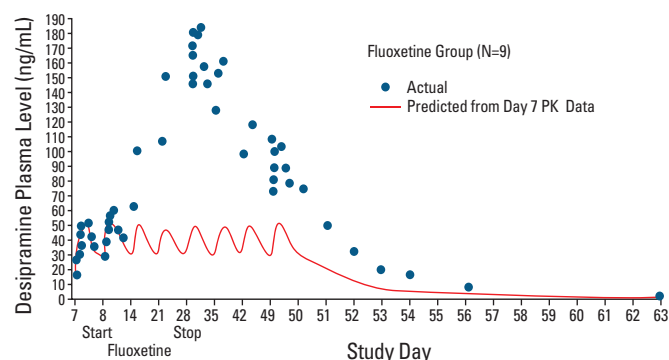
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Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 13, No 4. 2006.

On day 28, fluoxetine was discontinued but desipramine was continued at the same dose. Over the next 3 weeks, the desipramine levels fell as fluoxetine and norfluoxetine cleared from the body and CYP 2D6 inhibition was reversed, leading to an increase in desipramine clearance. Nevertheless, desipramine levels even 3 weeks after fluoxetine was discontinued were still double what they were before fluoxetine was added, because norfluoxetine was still present in the body and still inhibiting CYP 2D6-mediated clearance. This time course is consistent with the fact that the half-lives of fluoxetine and norfluoxetine in young healthy individuals (such as those in this study) are 2–4 days and 7–15 days, respectively. Of note, the average half-life of norfluoxetine in healthy individuals >65 years of age is 3 weeks; it takes an average of 4 months to reach steady-state once the drug is started in healthy older individuals and 4 months to completely clear once the drug is discontinued.<sup>92</sup>

While the study that provided the results in Figure 4 was about the effect of fluoxetine on CYP 2D6,<sup>91</sup> it graphically illustrates the point that the effect of a co-prescribed perpetrator drug (eg, fluoxetine) on the response to the victim drug (eg, desipramine) can continue to increase for weeks after the perpetrator has been started and can persist for weeks after the perpetrator has been stopped. Sometimes that is because the perpetrator has a long residual time in the body, as in the case of fluoxetine, and sometimes it is because the perpetrator's effect persists long after it has been cleared. An example of the latter would be the classic MAOIs, which cause irreversible inhibition of that enzyme; synthesis of new enzyme is, therefore, required to restore usual levels of activity once the classic MAOI has been stopped.<sup>92,93</sup> Thus, prescribers should wait >2

**FIGURE 4**  
**TIME COURSE: EFFECT OF FLUOXETINE ON CYP 2D6**  
**FUNCTION USING DESIPRAMINE AS THE PROBE DRUG<sup>91</sup>**



CYP=cytochrome P450.

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Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 13, No 4. 2006.

weeks after stopping an irreversible MAOI before starting a norepinephrine and serotonin agonist to minimize the risk of a hypertensive crisis or a serotonin syndrome, respectively. In a similar way, enzyme inducers have their induction effect immediately, though the time course for the maximum effect on increased clearance is not achieved until a new steady-state level of enzyme has been produced as a result of increased protein synthesis. For the same reason, the increased clearance persists for several weeks after the enzyme inducer has been stopped. These delayed onsets and offsets are not simply limited to pharmacokinetic interactions as witnessed by MAO inhibition (which is a pharmacodynamic interaction) but can be applied to all interactions in which the effect of the perpetrator persists for a sustained period after the perpetrator has been discontinued (eg, receptor supersensitivity or subsensitivity).

## HOW TO AVOID DRUG-DRUG INTERACTIONS

Table 16 summarizes the major principles relevant for minimizing the risk of DDIs. Next, the major tables for summarizing knowledge relevant to avoiding pharmacodynamic and pharmacokinetic DDIs are provided.

### Pharmacodynamic DDIs

Drugs are approved and generally considered from the perspective of their therapeutic use; however, they interact on the basis of their pharmacodynamics and pharmacokinetics. They also are frequently used for reasons other than their initial labeled indication. For example, most selective serotonin reuptake inhibitors were initially approved as antidepressants, but several have subsequently gained approved labeling for the treatment of a variety of anxiety disorders. In a similar way, a number of atypical antipsychotics have gained an approved indication for use in bipolar disorders. In recognition of these facts, the tables in this article outlining DDIs will consider these drugs in terms of their pharmacodynamics and pharmacokinetics rather than in terms of their labeled therapeutic indication.

Table 17 lists the neuropsychiatric medications to be covered in this article by their principal mechanism of action. Table 18 enumerates the pharmacodynamically mediated DDIs that can occur for each mechanism of action listed in Table 17. Using these tables together, the reader can determine the potential DDIs that can occur when any drug in Table 17 is used with another drug having a mechanism of action that can interact with its mechanism of action.<sup>80,94</sup>

A number of neuropsychiatric medications including tertiary amine TCAs and atypical antipsychotics affect more than one mechanism of action under clinically relevant dosing conditions. For this reason, Tables 9–11 were developed to show the relative effect of the most commonly used neuropsychiatric medications with multiple mechanisms of action.<sup>95-98</sup> In these tables, the most potent binding site of the drug was assigned the value of 1 and its relative binding affinity for other targets was expressed as its binding affinity for that target divided by its binding affinity for its most potent target. The resulting ratio reflects the increase in concentration needed for the drug to affect its less potent targets in relationship to its most potent target. For example, quetiapine binds most avidly to the  $\alpha_1$ -adrenergic receptor and binds almost as avidly to the histamine  $H_1$ -receptor, but requires a 23-fold increase in dose to bind to the dopamine  $D_2$  receptor (Table 10). That explains why low doses of quetiapine can be used for sedative effects but why higher doses are needed for antipsychotic efficacy. For the same reason, quetiapine can have the same pharmacodynamic DDIs as other potent  $H_1$ -receptor antagonists even though those other drugs might not have any efficacy as an antipsychotic medication.

The reader can use Tables 8–11 to determine how a multiple mechanism of action drug may have the potential for interacting pharmacodynamically by a mechanism other than its major presumed therapeutic mechanism (as listed in Table 17) and have an approximate understanding of the relative likelihood of such an interaction based on its relative binding affinity for secondary targets in relationship to the dose that is being used and the concentration that is likely being achieved in the patient. The reader can also use this information to determine whether he or she might wish to employ TDM to further establish the actual concentrations being achieved in their specific patient and relate that to both relative binding affinity for its multiple targets as well as relative to the concentration usually achieved on the dose being used. The clinician could use TDM to determine whether his or her specific patient has unusually fast or slow clearance relative to the usual clearance found in the registration trials and whether the patient is developing concentrations comparable to or much higher or lower than those found in registration trials.

## Pharmacokinetic Tables

These tables outline potential CYP enzyme-mediated DDIs. Parenthetically, CYP-mediated DDIs are the most common, clinically meaningful type of pharmacokinetic

DDIs. Table 19 lists which CYP enzymes metabolize which drugs and which drugs inhibit or induce specific CYP enzymes.<sup>35</sup> Using these tables and the logic outlined in Figure 3, the reader can predict the major potential CYP enzyme-mediated DDIs.<sup>59,79</sup>

## Pharmacokinetic Drug Interactions that are Not Metabolism-Based

This educational review restricted its discussion of pharmacokinetic DDIs to those mediated by CYP enzymes because of their clinical relevance. Nevertheless, there are other possible pharmacokinetic DDIs (Table 18)<sup>99</sup> worth briefly mentioning as follows: the chelation of drugs in the gastrointestinal tract by iron salts prescribed to treat anemia or by antacids with high aluminum content; interactions that occur prior to the administration of intravenous (IV) drugs due to the incompatibility of IV solutions; interaction with drug-secreting transporters that line the renal tubules and the blood-brain barrier (eg, lithium intoxication due to co-administration with ibuprofen and possibly other nonsteroidal anti-inflammatory drugs); and nutritional interactions that deplete the cofactors required for the phase II metabolism of some drugs (ie, reduced acetylation and glycosylation due to persistent hypoglycemia or clinically significant malnutrition).<sup>100</sup>

Important to note is that these mechanisms do not include protein binding (or “bumping”) interactions in which a perpetrator displaces a victim drug from serum proteins such as albumin or  $\alpha_1$  acid glycoprotein. This mechanism virtually never mediates a DDI of clinical significance, although it is well ensconced in the literature and the minds of physicians. This mechanism is virtually never clinically significant, because the resulting increased free drug persists for a short and clinically insignificant period before the access of the same free drug to elimination mechanisms, such as enzymes transporters, reduces the free concentration to a new equilibrium close to the original.<sup>101</sup>

Appendix I lists Web sites that the reader can use to find additional information.<sup>35,59,102-106</sup> Web sites have the advantage of being regularly updated so that the information will stay current long after this article has been published. Appendix II lists software packages and their current limitations are in Table 20.<sup>107-111</sup>

One major limitation is that there are no standard guidelines for producing such drug alert systems in terms of what constitutes sufficient evidence to list an interaction as possible. Thus, software packages can list interactions based on theory rather than fact or based on a single case report of dubious validity. This situation, in turn, can cause a high

rate of false positive alerts (an “overly sensitive” approach) that can, ironically, lead the prescriber to ignore the system (ie, “the boy who cried wolf”).

Other systems may only include DDIs which have been demonstrated to occur in a formal study and do not generalize the interaction to other drugs with the same mechanism mediating the DDI. This situation leads to false negatives. An example is a system that reports fluoxetine’s ability to increase the level of desipramine (Figure 4) but does not warn about bupropion, which, at a dose of 300 mg/day, inhibits CYP 2D6 to a degree comparable to that of fluoxetine 20 mg/day.<sup>112</sup>

Another limitation is that most drug alert systems only consider the effect of drug A on drug B, whereas many patients are on multiple drugs that may interact in complex ways. An example would be a patient who is taking a drug equally cleared by CYP 2D6 and CYP 3A. That patient may not be at substantial risk for toxicity when treated with either a CYP 2D6 or CYP 3A inhibitor alone but may be if treated with both inhibitors at the same time.<sup>112</sup> Most systems focus on pharmacodynamic or pharmacokinetic DDIs as if they were mutually exclusive when, in fact, both can occur simultaneously; hence, amplifying each other.<sup>12,25</sup>

Current DDI alert systems may alert but provide little or no guidance about what the prescriber can do to minimize risk of the interactions, such as finding a substitute for either the perpetrator or the victim drug, adjusting the dosage of the victim drug (in the case of CYP enzyme-mediated DDI), or specially monitoring (eg, TDM or electrocardiograms).

However, the greatest limitation is knowledge. While there are 520 quadrillion possible combinations of up to five drugs using the number of drugs in the 2006 *Physicians’ Desk Reference*,<sup>113</sup> there are only approximately 700 published formal DDI studies, and virtually all of those are constrained to the effect of one drug on another drug. In fact, virtually all clinically significant DDIs were first discovered by astute and conscientious clinicians who published their findings as case reports in medical literature. Those reports served as a stimulus for scientific study,

which uncovered the pharmacologic basis for the interactions and led to generalizable knowledge. For this reason, the authors encourage the readers to write up their cases and publish them in the medical literature, as well as to use the adverse drug reaction reporting system developed by the FDA (Table 21).<sup>114,115</sup>

Given the above limitations, software packages do not replace the educated, astute, and conscientious prescriber who remains the major safeguard against the occurrence of serious untoward interactions. The authors hope that this educational review can serve as an aid to these prescribers in providing safe and effective treatment for their patients.

## CONCLUSION

DDIs are common, important, and growing in frequency in concert with both the increasing number of pharmaceuticals available and the number of patients on multiple medications. Each year more medications are added to the available armamentarium. There is an increasing use of multiple medications to treat patients, particularly as the focus of treatment has shifted from short-term therapy of acute illnesses (eg, bacterial infections) to long-term treatment and/or prevention of chronic illnesses (eg, schizophrenia and Alzheimer’s disease, respectively).

To avoid unintended and untoward DDIs, the prescriber must understand fundamental principles of pharmacology and good clinical management. The prescriber must have knowledge of the pharmacodynamic and pharmacokinetics of the drugs that his or her patients are taking. This educational review has addressed these principles and presented tables summarizing the major pharmacodynamic and pharmacokinetic interactions affecting and/or caused by commonly used neuropsychiatric medications. Additionally, appendices were provided listing Web sites, books, and cards containing additional information on specific DDIs. In addition, these Web sites are updated on a regular basis so the reader can stay informed of the rapid developments concerning DDIs. **PP**

TABLE 1

**DRUG APPROVALS BY THE US FDA BETWEEN 2003 AND 2005****Cardiology/Vascular Diseases**

- Rosuvastatin calcium (Crestor); For the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; AstraZeneca; Approved August 2003.
- Vardenafil (Levitra); For the treatment of erectile dysfunction related to sexual activity in men; Bayer, GlaxoSmithKline; Approved September 2003.
- Tadalafil (Cialis); Oral agent for the treatment for erectile dysfunction; Eli Lilly; Approved December 2003.
- Amlodipine/atorvastatin (Caduet); For the treatment of hypertension, chronic stable angina and vasospastic angina; Pfizer; Approved January 2004.
- Isosorbide dinitrate/hydralazine hydrochloride (BiDil); For the treatment of heart failure in black patients; NitroMed; Approved June 2005.

**Dermatology**

- Alefacept (Amevive); For moderate-to-severe chronic plaque psoriasis; Biogen; Approved January 2003.
- Azelaic acid (Finacea) Gel, 15%; Gel formulation for the treatment of rosacea; Berlex Laboratories; January 2003.

**Endocrinology**

- Iaronidase (Aldurazyme); For the treatment of Mucopolysaccharidosis I (MPS I) in subjects aged 5–65; Genzyme; Approved May 2003.
- Agalsidase beta (Fabrazyme); For the treatment of Fabry disease in adult patients; Genzyme; Approved April 2003.
- Pegvisomant (Somavert); Injectable formulation for the treatment of acromegaly; Pharmacia; Approved March 2003.
- Exenatide (Byetta); For the adjunctive treatment of Type 2 diabetes mellitus; Amylin/Eli Lilly; Approved April 2005.

**Hematology**

- $\alpha_1$ -proteinase inhibitor (Zemaira); For the treatment of  $\alpha_1$ -proteinase inhibitor deficiency ( $\alpha_1$ ) and emphysema; Aventis Behring; Approved July 2003.
- Azacitidine (Vidaza); For the treatment of several myelodysplastic syndrome subtypes including refractory and chronic myelomonocytic leukemias; Pharmion Corporation; Approved May 2004.

**Immunology/Infectious Diseases**

- Influenza Virus Vaccine (FluMist); For the prevention of disease caused by influenza A and B viruses; MedImmune; Approved June 2003.
- Enfuvirtide (Fuzeon); For the treatment of HIV-1 infection in combination with other antiretroviral agents; Trimeris, Roche; Approved March 2003.
- Fosamprenavir calcium (Lexiva); For the treatment of HIV infection in adults in combination with other antiretroviral agents; GlaxoSmithKline; Approved October 2003.
- Atazanavir sulfate (Reyataz); For the treatment of HIV-1 infection in combination with other antiretroviral agents; Bristol-Myers Squibb; Approved July 2003.
- Telithromycin (Ketek); For the treatment of infections caused by bronchitis, bacterial sinusitis and community-acquired pneumonia; Aventis Pharmaceuticals; Approved April 2004.

- Tinidazole (Tindamax); For the treatment of microbial infections, including trichomoniasis, giardiasis, and amebiasis; Presutti Laboratories; Approved May 2004.
- Rifaximin (Xifaxan); For the treatment of Travelers' diarrhea caused by noninvasive strains of Escherichia coli; Salix Pharmaceuticals; Approved May 2004.
- Tipranavir (Aptivus); For the adjunctive treatment of HIV-1 infections; Boehringer Ingelheim; Approved June 2005.
- Entecavir (Baraclude); For the treatment of chronic hepatitis B infections with evidence of active viral replication; Bristol-Myers Squibb; Approved March 2005.

**Musculoskeletal**

- Ibandronate (Boniva); For the treatment and prevention of osteoporosis; Roche/GlaxoSmithKline; Approved May 2003.

**Nephrology/Urology**

- Oxybutynin transdermal system (Oxytrol); For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency; Watson Pharmaceuticals; Approved March 2003.
- Alfuzosin HCl extended-release tablets (UroXatral); For the treatment of the signs and symptoms of benign prostatic hyperplasia; Sanofi-Synthelabo; Approved June 2003.
- lanthanum carbonate (Fosrenol); For the treatment of hyperphosphatemia related to kidney dysfunction; Shire Pharmaceuticals; Approved October 2004.
- Trosipium chloride (Sanctura); For the treatment of overactive bladder with symptoms of urge urinary incontinence; Indevus Pharmaceuticals; Approved May, 2004.
- Cinacalcet (Sensipar); For the treatment of secondary hyperparathyroidism and hypercalcemia in parathyroid carcinoma patients; Amgen; Approved March 2004.
- Solifenacin succinate (Vesicare); For the treatment of overactive bladder with symptoms of urge urinary incontinence; Yamanouchi, GlaxoSmithKline; Approved November, 2004.

**Neurology**

- Memantine HCl (Namenda); For the treatment of moderate-to-severe dementia of the Alzheimer's type; Forest Laboratories; Approved October 2003.
- Apomorphine hydrochloride (Apokyn); For the treatment of acute, intermittent hypomobility episodes associated with advanced Parkinson's disease; Mylan Bertek Pharmaceuticals; Approved April 2004.
- Natalizumab (Tysabri); For the treatment of relapsing forms of multiple sclerosis; Elan Pharmaceuticals/Biogen Idec; Approved November 2004; – **SUSPENDED FEBRUARY 2005**

**Obstetrics/Gynecology**

- Estradiol gel 0.06% (EstroGel); For the treatment of vasomotor symptoms and vulvar and vaginal atrophy associated with menopause; Solvay Pharmaceuticals; Approved April 2004.

**Oncology**

- Palonosetron (Aloxi); For the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy; MGI Pharma, Helsinn Healthcare; Approved August 2003.

(cont. on page 50)

**TABLE 1 (CONT.)  
DRUG APPROVALS BY THE US FDA BETWEEN 2003 AND 2005**

**Oncology**

- **Tositumomab (Bexxar);** For the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma following chemotherapy relapse; Corixa; Approved June 2003.
- **Aprepitant (Emend);** For the treatment of nausea and vomiting associated with chemotherapy; Merck; Approved March 2003.
- **Gefitinib (Iressa);** For the second-line treatment of non-small-cell lung cancer; AstraZeneca; Approved May 2003.
- **Abarelix as an injectable suspension (Plenaxis);** For treatment of advanced prostate cancer; Praecis Pharmaceuticals; Approved December 2003.
- **Bortezomib (Velcade);** Injectable agent for the treatment of multiple myeloma patients who have received at least two prior therapies; Millennium Pharmaceuticals; Approved May 2003.
- **Pemetrexed for injection (Alimta);** For the treatment of malignant pleural mesothelioma; Eli Lilly; Approved February 2004.
- **Bevacizumab (Avastin);** For the treatment of metastatic carcinoma of the colon or rectum; Genentech; Approved February 2004.
- **Clofarabine (Clolar);** For the treatment of acute lymphoblastic leukemia in pediatric patients; Genzyme; Approved December, 2004.
- **Cetuximab (Erbix);** For the treatment of EGFR-expressing, metastatic colorectal cancer; Imclone, Bristol-Myers Squibb; Approved February 2004.
- **Erlotinib (Tarceva);** For the treatment of advanced refractory metastatic non-small cell lung cancer; Genentech, OSI Pharmaceuticals; Approved November, 2004.

**Ophthalmology**

- **Pegaptanib (Macugen);** For the treatment of wet age-related macular degeneration; Pfizer/Eyetech Pharmaceuticals; Approved December 2004.

**Psychiatry**

- **Acamprosate calcium (Campral);** For the treatment of alcohol dependence and the maintenance of alcohol abstinence; Forest Laboratories; Approved August 2004.
- **Duloxetine (Cymbalta);** For the treatment of MDD; Eli Lilly; Approved August 2004.
- **Eszopiclone (Lunesta);** For the treatment of insomnia and sleep maintenance; Sepracor; Approved December 2004.
- **Ramelteon (Rozerem);** For the treatment of sleep-onset insomnia; Takeda; Approved July 2005.

**Respiratory Diseases**

- **Tiotropium bromide (Spiriva HandiHaler);** For the treatment of bronchospasm associated with chronic obstructive pulmonary disease; Boehringer Ingelheim; Approved February 2004.

**Rheumatology**

- **Rofecoxib (Vioxx);** For the treatment of rheumatoid arthritis; Merck; Approved April 2002 – **WITHDRAWN OCTOBER 2004**

US FDA=United States Food and Drug Administration; HIV=human immunodeficiency virus; EGFR=epidermal growth factor receptor; MDD=major depressive disorder. Reproduced with permission. ©Preskorn.

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**TABLE 2  
THE POTENTIAL FOR DIFFERENT, NEWER ANTIDEPRESSANT TO BE THE PERPETRATOR OF A DDI MEDIATED BY EFFECTS ON CYP ENZYMES<sup>38</sup>**

<b>SSRIs (Trade name)</b>	<b>1A2</b>	<b>2C9/10</b>	<b>2C19</b>	<b>2D6</b>	<b>3A3/4</b>
Citalopram (Celexa)	•	•	•	++	•
Escitalopram (Lexapro)	•	•	•	++	•
Fluoxetine (Prozac)	•	++	++	+++	+
Fluvoxamine (Luvox)	+++	+++	+++	•	++
Sertraline (Zoloft)	•	•	•	+	•
Paroxetine (Paxil, Paxil CR)	•	•	•	+++	•
<b>SNRIs</b>	<b>1A2</b>	<b>2C9/10</b>	<b>2C19</b>	<b>2D6</b>	<b>3A3/4</b>
Duloxetine (Cymbalta)	•	•	•	++	•
Venlafaxine ER (Effexor XR)	•	•	•	•	•
<b>Newer Antidepressants</b>	<b>1A2</b>	<b>2C9/10</b>	<b>2C19</b>	<b>2D6</b>	<b>3A4/4</b>
Bupropion (Wellbutrin)	?	?	?	+++	?
Nefazodone (Serzone)	•	•	•	•	+++

\* Percent increase in plasma levels of a coadministered drug dependent on this CYP enzyme for its clearance: •=no or minimal effect (< 20%); ++=moderate effect (50–150%); +=mild effect (20–50%); +++=substantial effect (>150%); ?=unknown.

DDI=drug-drug interaction; CYP=cytochrome P450; SSRIs=selective serotonin reuptake inhibitors; SNRIs=selective norepinephrine reuptake inhibitors; CR=controlled release; XR=extended release.

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Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 13, No 4. 2006.

**TABLE 3  
MULTIPLE MEDICATION USE IN PATIENTS SEEN IN THE VETERANS AFFAIRS HEALTHCARE SYSTEM AS A FUNCTION OF AGE AND ANTIDEPRESSANT DRUG USE<sup>56-58</sup>**

<b>&lt;60 Age (years)</b>	<b>Not on an Antidepressant</b>	<b>On an Antidepressant</b>
Median number of meds.	2	5
% on a unique regimen	62	83
<b>&lt;60 Age (years)</b>		
Median number of meds.	4	6
% on a unique regimen	75	96

meds=medications.

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**TABLE 4**  
**PERCENTAGE (%) OF PATIENTS ON ANTIDEPRESSANTS THAT HAVE A POTENTIAL TO EXPERIENCE A DDI AS A FUNCTION OF TREATMENT SETTING<sup>3,9,60</sup>**

	Number of Patients	% on an Antidepressant	% on an Antidepressant Plus >3 Other Medications
Primary care	2,045	28%	34%
Psychiatry clinic	224	29%	30%
VA Medical Centers and clinics	1,076	7%	68%
HIV clinic	66	1%	77%

DDI=drug-drug interaction; VA=Veterans Affairs; HIV=human immunodeficiency virus.  
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**TABLE 5**  
**THE “AVOID” ALGORITHM**

- Allergies: Are there any medicines we should not give you for any reason?
- Vitamins and Herbs: Do you take any herbal medicines?
- OTC: Do you take any over-the-counter medicines?
- Interactions: Use a database to check for interactions.
- Dependence: Are there any medicines that you feel we should not discontinue? If so, why?

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**TABLE 6**  
**PERSONAL FORMULARY: ESSENTIAL ELEMENTS OF KNOWLEDGE FOR EACH DRUG**

*Know the dosage forms available for the drugs prescribed*

**Pharmacokinetic Data**

- Enzymes or transporters responsible for elimination
- Half-life and effect of renal or liver disease on half-life
- Pharmacokinetic variability amongst ethnic groups

**Clinical Trial data**

- An ongoing familiarity with all major clinical trials and studies

**Pharmacodynamic Data**

- Receptor affinity and specificity relative to other drugs
- Clinically important adverse (“side”) effects

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**TABLE 7**  
**EXAMPLES OF SSRI WITH DIFFERENT BRAND NAMES THROUGHOUT THE WORLD<sup>79</sup>**

Country	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Argentina	Humorap, Psiconor, Seropram, Zentius	Alental, Animex-on, Captation, Eburnate, Equilibrane, Faboxetina, Foxetin, Lapsus, Mitilase, Neupwax, Prozac, Saurat	Luvox	Afenexil, Aropax, Datevan, Meplar, Neurotrox, Olane, Pamoxet, Paxil, Psicoasten, Sicopax, Tiarix	Anilar, Atenix, Bicromil, Insertec, Irradial, Serlina, Zoloft
Australia	Celapram, Cipramil, Talam, Talohexal	Auscap, Erocap, Fluohexal, Lovan, Prozac, Zactin	Faverin, Luvox, Movox	Aropax, Oxetine, Paxtine, Roxatine	Zoloft
Austria	Citarcana, Citalhexa, Citalon, Citor, Pram, Seralgan	Felicium, Fluctine, Floxibene, Fluoxistad, Fluoxityrol, Flux, Fluxil, FluxoMed, Mutan, NuFluo, Positivum	Felixsan, Floxyfral	Allenopar, Aparo, Ennos, Glaxopar, Paluxetil, Parocetan, Paroglax, Paroxat, Seroxat	Gladem, Tresleen, Zoloft
Belgium	Cipramil	Fontex, Prozac	Dumirox, Floxyfral	Aropax, Seroxat	Serlain
Brazil	Cipramil, Denyl	Daforin, Deprax, Depress, Eufor, Fluxene, Nortec, Prozac, Prozen, Psiquial, Verotina	Luvox	Aropax, Cebrilin, Pondera	Novativ, Sercerin, Tolrest, Zoloft
Canada	Celexa	FXT, Prozac	Luvox, Riva-Fluvox	Paxil	Zoloft
Chile	Actipram, Cimal, Cipramil, Finap, Prisma, Semax, Setronil, Temperax, Zebrak, Zentius	Actan, Anisimol, Clinium, Dominium, Pragmaten, Prozac, Seroscand, Sostac, Tremafarm	Luvox	Aroxat, Bectam, Posivyl, Seretran, Traviata	Altruline, Deprax, Eleval, Emergen, Implicane, Lowfin, Sedoran, Servo

(cont. on page 52)

TABLE 7 (CONT.)

EXAMPLES OF SSRI'S WITH DIFFERENT BRAND NAMES THROUGHOUT THE WORLD<sup>79</sup>

Country	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Czech Rep.	Citalec	Deprenon, Deprex, Floxet, Fluminex, Fluocim, Fluogal, Fluoxin, Fluval, Fluxonil, Framex, Magrilan, Milezin, Portal, Prozac	Fevarin	Seroxat	Serlift, Zoloft
Denmark	Citadur, Citaham	Afeksin, Flutin, Fluxantin, Folizol, Fondur, Fonigen, Fontex, Fonzac, Nycoflox	Fevarin	Oxetine, Serodur, Seroxat	Zoloft
Finland	Emocal, Sepram	Fluoxal, Fluxantin, Fontex, Seromex, Seronil	Fevarin, Fluvosol	Optipar, Seroxat	Zoloft
France	Seropram	Prozac	Floxyfral	Deroxat, Divarius	Zoloft
Germany	Cilex, Cipramil, Citadura, Sepram, Serital	Fluctin, Fluneurin, Fluox, Fluoxa, FluoxeLich, Fluoxemerck, Fluoxe-Q, Fluoxgamma, Fluox-Puren, Fluxet, Fysionorm, Motivone	Desifluvoxamin, Fevarin, Fluvohexal, Fluvoxadura, Myroxim	Euplix, Oxet, ParoLich, Paroxat, Paroxedura, Seroxat, Tagonis	Gladem, Zoloft
Greece	Seropram	Dagrilan, Dinalexin, Exostrept, Flonital, Fluxadir, Fokeston, Ladose, Orthon, Sartuzin, Stephadilat-S, Stressless, Zinovat	Dumyrox, Myroxine	Seroxat	Zoloft
Hong Kong	Cipram	Atd, CP-Fluoxet, Deprexin, Fluxetin, Fluxil, Magrilan, Nopres, Plazeron, Provatine, Prozac	Faverin	Seroxat	Zoloft
Hungary	Seropram	Deprexin, Fefluzin, Floxet, Portal, Prozac	Fevarin	Paroxat, Rexetin, Seroxat	Stimuloton, Zoloft
Ireland	Ciprager, Ciprapine, Citrol	Affex, Biozac, Gerozac, Norzac, Prozac, Prozamel, Prozatan, Prozit	Faverin	Meloxat, Paroser, Parox, Seroxat	Lustral
Israel	Cipramil, Recital	Affectine, Flutine, Prizma, Prozac	Favoxil	Paxxet, Seroxat	Lustral
Italy	Elopram, Seropram	Azur, Clexiclor, Cloriflox, Deprexin, Diesan, Flotina, Fluoxeren, Fluoxin, Grinflux, Iboxetin, Prozac, Serezac, Xeredien, Zaflux	Dumirox, Fevarin, Maveral	DaparoX, Eutimil, Sereupin, Seroxat	Serad, Tatig Zoloft
Malaysia	Cipram	Prozac	Luvox	Seroxat	Serlift, Zoloft
Mexico	Seropram	Auroken, Axtin, Flocet, Florexal, Fluoxac, Prozac, Siquial	Luvox	Aropax, Paxil	Altruline
Netherlands	Ciprapine, Lontax	Fluoxstad, Flustad, Prozac	Fevarin	Seroxat	Asentra, Zoloft
Norway	Cipramil, Desital	Fontex, Nycoflox	Fevarin	Seroxat	Zoloft
Portugal	Cipramil	Digassim, Nodepe, Prozac, Pspipax, Salipax, Selectus, Tuneluz	Dumyrox	Denerval, Oxepar, Paxetil, Seroxat	Zoloft
Singapore	Cipram	Deprexin, Fluxetil, Fluxetin, Magrilan, Prodep, Prozac, Zactin	Faverin	Seroxat	Zoloft
South Afr	Cilift, Cipramil, Talomil	Deprozan, Lorien, Nuzak, Prohexal, Prozac, Prozyn, Ranflocs, Sanzur	Luvox	Aropax	Serlife, Zoloft
Spain	Genprol, Prisdal, Seropram	Adofen, Astrin, Docutrix, Lecimar, Luramon, Nodepe, Prozac, Reneuron, Zaxetina	Dumirox	Aropax, Casbol, Frosinor, Motivan, Seroxat, Xetin	Aremis, Besitran, Sealdin
Sweden	Citavie	Fluxantin, Fontex	Fevarin	Euplix, Paroxiflex, Seroxat	Zoloft
Switzerland	Alutan, Claropram	Fluctine, Fluocin, Fluoxifar, Fluox-basan, Flusol	Flox-ex, Floxyfral	Deroxat, Parexat	Gladem, Zoloft
Thailand	Cipram	Actisac, Atd, Deproxin, Flumed, Fluoxine, Flusac, Flutine, Fluxetil, Fluxetin, Fluzac, Hapilux, Loxetine, Magrilan, Oxetine, Oxsac, Prodep, Prozac, Unprozy	Faverin, Fluvoxin	Seroxat	Zoloft
Turkey	Cipram, Citol	Depreks, Prozac	Faverin	Paxil, Seroxat	Lustral
UK	Cipramil	Felicium, Prozac, Prozit,	Faverin	Seroxat	Lustral
US	Celexa	Prozac, Sarafem	Luvox	Paxil, Pexeva	Zoloft

SSRIs=selective serotonin reuptake inhibitors; UK=United Kingdom; US=United States.

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TABLE 8

**CLASSIFICATION OF NEUROPSYCHIATRIC MEDICATIONS BASED ON THEIR PRINCIPLE MECHANISMS OF ACTION<sup>80</sup>****Muscarinic Acetylcholine Receptor Antagonism**

Atropine	Orphenadrine (eg, Norflex)
Belladonna	Oxybutynin (eg, Ditropan)
Benzotropine (Cogentin)	Procyclidine (Kemadrin)
Biperiden (Akineton)	Propanthethine (eg, Pro-Banthine)
Clidinium (Quarzan)	Scopolamine (eg, Sopace)
Dicyclomine (eg, Bentyl)	Solifenacin (Vesicare)
Glycopyrrolate (eg, Robinul)	Trospium (Sancturn)
Hyoscyamine (eg, Anaspaz)	Tolterodine (Detrol)
Mepenzolate (Cantil)	Trihexyphenidyl (Artane)
Methscopolamine (Pamine)	

Also includes: A number of low-potency phenothiazines (See the class below labeled: "5-HT<sub>2A</sub> and D<sub>2</sub> antagonists with other effects"), a number of tertiary amine TCAs and related antidepressants (See the class below labeled: "Serotonin and norepinephrine reuptake inhibition with other effects"), clozapine, olanzapine, and protriptyline.

**Cholinesterase Inhibition**

Biogenic amine (effects on dopamine, norepinephrine, and serotonin)	
Donepezil (Aricept)	Rivastigmine (Exelon)
Galantamine (Reminyl)	

**Catechol-O-Methyltransferase Inhibition**

Entacapone (Comtan)	Selegiline (Eldepryl)
Isocarboxazid (Marplan)	Tolcapone (Tasmar)

**Monoamine Oxidase Inhibition**

Phenelzine (Nardil)	Tranylcypromine (Parnate)
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**Biogenic Amine Release**

Release: Classically NE>DA>SE but rank order of effects on these neurotransmitters may vary amongst the different drugs in this class.

Amphetamines (eg, Desoxy)	Methamphetamine
Benzphetamine (Didrex)	Methylphenidate (eg, Ritalin)
Dextroamphetamine (eg, Dexedrine)	Phendimetrazine (eg, Prelu-2)
Diethylpropion (eg, Tenuate)	Phentermine (eg, Ionamin)

**Dopamine-2 (D<sub>2</sub>) Agonism**

Bromocriptine [+partial D <sub>1</sub> agonism]: (Parlodel)	Pramipexole [+ D <sub>3</sub> agonism but no D <sub>1</sub> activity]: (Mirapex)
Pergolide [+D <sub>1</sub> agonism]: (Permax)	Ropinirole [+ D <sub>3</sub> agonism but no D <sub>1</sub> activity]: (Requip)

**Dopamine Uptake Inhibition**

Amantadine (Symmetrel)	Cocaine
Benzphetamine (Didrex)	Methamphetamine (eg, Desoxy)
Bupropion (Wellbutrin, Zyban):	
See Table 14 for relative effects on neuroreceptors	

**Dopamine:** Levodopa (dopamine precursor, dopamine agonism [general] component of Sinemet).

**Dopa Decarboxylase Inhibitor**

Carbidopa (Component of Sinemet)

**Selective D<sub>2</sub> Receptor Antagonism**

Fluphenazine (eg, Prolixin)	Piperazine (Entacyl)
Haloperidol (eg, Haldol):	Trifluoperazine (eg, Stelazine)
Perphenazine (eg, Trilafon)	Triflupromazine (eg, Vesprin)
Pimozide (Orap)	

See Table 9 and 10 for relative effects on neuroreceptors.

**D<sub>2</sub> Receptor Partial Agonism**

Aripiprazole (Abilify)

See Table 12 for relative effects on neuroreceptors.

**D<sub>2</sub> Receptor Antagonism Plus Multiple Other Effects**

See 5-HT<sub>2A</sub>, D<sub>2</sub> and multiple other effects below.

**Ethanol:** Solubilizes electrically excitable membranes.

**GABA:** Barbiturates enhance the binding of GABA to pentobarbital (eg, Nembutal) GABA<sub>A</sub> receptors and promote rather than phenobarbital displace the binding of benzodiazepines

Amobarbital (Amytal)	Primidone (Mysoline)
Butabital (eg, Butisol)	Secobarbital (Seconal)

**Barbiturate-Like Drugs**

Chloral hydrate (eg, Aquachloral)	Mephobarbital (Mebaral)
Ethchlorvynol (Placidyl)	Metharbital

**Benzodiazepine Binding Site Agonism**

Alprazolam (eg, Xanax)	Lorazepam (eg, Ativan)
Chlordiazepoxide (eg, Librium)	Midazolam (eg, Versed)
Clonazepam (eg, Klonopin)	Prazepam (Centrax)
Clorazepate (eg, Tranxene)	Quazepam (Doral)
Diazepam (eg, Valium)	Temazepam (eg, Restoril)
Estazolam (eg, ProSom)	Triazolam (eg, Halcion)
Flurazepam (eg, Dalmane)	Zolpidem (Ambien)
Halazepam (Paxipam)	

**Benzodiazepine-Like Drug:** Meprobamate (eg, Miltown)

**GABA Transaminase Inhibition and Stimulation of Glutamic Acid Decarboxylase**

Divalproex sodium (Depakote)	Valproate sodium (Depacon)
Valproic acid (Depakene)	

**Promotion of Nonvesicular Release of GABA**

Gabapentin (Neurotonin)

**Glutamate (N-methyl-D-aspartate receptor)**

Memantine (Nemeda)

**Herbals**

Ginkgo biloba	Ginseng
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**Histamine (Centrally Active) (H<sub>1</sub>) Antagonism**

Chlorpheniramine	Hydroxyzine (Atarax)
Cyclobenzaprine (Flexeril)	St. John's Wort

(cont. on page 54)

TABLE 8 (CONT.)

## CLASSIFICATION OF NEUROPSYCHIATRIC MEDICATIONS BASED ON THEIR PRINCIPLE MECHANISM OF ACTION<sup>78</sup>

### Diphenhydramine (Benadryl)

Also includes: a number of low potency phenothiazines (See the class below labeled: "5-HT<sub>2A</sub> and D<sub>2</sub> antagonists with other effects"), a number of tertiary amine TCA and related antidepressants (See the class below labeled: "Serotonin and norepinephrine reuptake inhibition with other effects"), clozapine, olanzapine, maprotiline, mirtazapine, nefazodone, and quetiapine.

### Ion Channel Inhibition

Carbamazepine (eg, Tegretol) slows the recovery of voltage-activated Na<sup>+</sup> channels.

Dantrolene (Dantrium) interferes with the release of Ca<sup>++</sup> from sarcoplasmic reticulum.

Felbamate (Felbatol) inhibits NMDA-evoked responses and potentiates GABA-evoked responses.

Lithium (eg, Eskalith) substitutes for multiple ions.

Lamotrigine (Lamictal) [has the effects of carbamazepine] plus inhibition of glutamate release.

Mephenytoin (Mesantoin) slows recovery of voltage-activated Na<sup>+</sup> channels.

Phenytoin (eg, Dilantin) slows recovery of voltage-activated Na<sup>+</sup> channels.

Topiramate (Topamax) reduces voltage-gated Na<sup>+</sup> currents, enhances postsynaptic GABA<sub>A</sub> receptor currents, and limits activation of AMPA-kainate subtypes of the glutamate receptor.

Other CNS drugs with potentially clinically relevant effects on ion channels at usual concentrations include: a number of low potency phenothiazines (See the class below labeled: "5-HT<sub>2A</sub> and D<sub>2</sub> antagonists with other effects"), a number of tertiary amine TCAs and related antidepressants (See the class below labeled: "Serotonin and norepinephrine reuptake inhibition with other effects"), clozapine pimozone, and ziprasidone. Thioridazine has a black box warning because of such effects.

### Norepinephrine

#### α<sub>1</sub> Antagonism

This mechanism is not known to mediate any desired CNS effect, thus no neuro-psychiatric medications were developed to have only this specific mechanism of action. Nevertheless, several neuropsychiatric medications do achieve concentrations under clinically relevant dosing conditions, which block this receptor. These medications include: amitriptyline, chlorpromazine, clozapine, quetiapine, nefazodone, risperidone, thioridazine, and trazodone. See tables 9-11 for relative binding affinities to this receptor by these drugs.

#### α<sub>2</sub> Agonism

Clonidine (eg, Catapres)

#### Norepinephrine Uptake Pump Inhibition

Atomoxetine (Strattera)	Nortriptyline (eg, Pamelor)
Cocaine	Phentermine (eg, Ionamine)
Desipramine (eg, Norpramin)	Protriptyline (eg, Vivactil)
Maprotiline (eg, Ludiomil)	Reboxetine (Vespar)

#### Dual Norepinephrine and Serotonin (NE > SE) Uptake Pump Inhibition Plus Other Actions

Amitriptyline (eg, Elavil)	Doxepin (eg, Sinequan)
Amoxapine (eg, Ascendin)	Imipramine (eg, Tofranil)
Clomipramine (eg, Anafril)	Trimipramine (eg, Surmontil)

### Opiate Receptors

Alfentanil (Alfental)	Nalbuphine (eg, Nubain)
Buprenorphine (Buprenex)	Opium (eg, Paregoric)
Codeine	Oxycodone (Roxicodone)
Fentanyl (eg, Sublimaze)	Pentazocine (eg, Talwin)
Hydrocodone (eg, Vicodin)	Propoxyphene (eg, Darvon)
Hydromorphone (eg, Dilaudid)	Sufentanil (eg, Sufenta)
Meperidine (eg, Demerol)	Tramadol (Ultram)
Methadone (eg, Dolophine)	

### Serotonin

#### 5-HT<sub>1A</sub> Partial Agonism

Buspirone (eg, Buspar)

#### 5-HT<sub>1B/D</sub> Agonism

Ergotamine (eg, Ergomar)	Dihydroergotamine (D.H. E. 45)
Naratriptan (Amerge)	Sumatriptan (Imitrex)
Rizatriptan (Maxalt)	Zolmitriptan (Zomig)

#### 5-HT<sub>2</sub> Receptor Antagonism

Cyproheptadine (Periactin)	Nefazodone (Serzone)*
Methysergide (Sansert)	Trazodone (eg, Desyrel)*
Mirtazapine (Remeron)*	

\*See Table 11 for relative effects on neuroreceptors.

#### 5-HT<sub>2A</sub> and D<sub>2</sub> Receptor Antagonism

Olanzapine (Zyprexa)	Risperidone (Risperdal)
Ziprasidone (Geodon)	

See Table 9 for relative effects on neuroreceptors for all of these drugs.

#### 5-HT<sub>2A</sub>, D<sub>2</sub>, and Multiple Other Receptor Antagonism

Chlorpromazine (eg, Thorazine)*	Prochlorperazine (eg, Compazine)
Clozapine (eg, Clozaril)*	Promethazine (eg, Phenergan)
Loxapine (eg, Loxitane)*	Promazine (eg, Sparine)
Mesoridazine (eg, Serentil)	Thiethylperazine (Torecan)
Propiomazine (Largon)	Thioridazine (eg, Mellaril)*

\*See Tables 9 and 10 for relative effects on neuroreceptors.

#### Serotonin Uptake Inhibition

Dexfenfluramine (Redux)	Fenfluramine (Pondimin)
-------------------------	-------------------------

#### Selective Serotonin Uptake Inhibition

Citalopram (Celexa)	Paroxetine (Paxil)
Escitalopram (Lexapro)	Sertraline (Zoloft)
Fluoxetine (eg, Prozac)	Sibutramine (Meridia)
Fluvoxamine (eg, Luvox)	

#### Dual Serotonin and Norepinephrine (5-HT<sub>2</sub>/NE) Uptake Pump Inhibition

Duloxetine (Cymbalta)	Sibutramine (Meridia)
Venlafaxine (Effexor)	

TCAs=tricyclic antidepressants; NE=norepinephrine; DA=dopamine; SE=serotonin; GABA=γ-aminobutyric acid; NMDA=N-methyl-D-aspartate; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CNS=central nervous system.

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TABLE 9

RELATIVE BINDING AFFINITY OF SELECTED, NEWER ANTIPSYCHOTICS FOR SPECIFIC NEURORECEPTORS<sup>51-55,80</sup>

Drug	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	D <sub>4</sub>	5-HT <sub>1A</sub>	5-HT <sub>2A</sub>	5-HT <sub>2C</sub>	α <sub>1</sub>	H <sub>1</sub>	M <sub>1</sub>
Aripiprazole	780	1*	2	129	5	10	44	138	180	>1,000
Clozapine	45	66	250	18	460	8	8	4	3	1
Haloperidol	300	1	3	4	>1,000	64	>10,000	9	629	>2,000
Olanzapine	16	6	25	24	>5,000	2	12	9	4	1
Quetiapine	65	23	49	230	400	42	214	1	2	17
Risperidone	614	6	14	13	300	1	36	1	29	>10,000
Ziprasidone	>1,000	13	18	18	8	1	2.5	28	125	>1,000

In this table, the most potent site of action for a specific drug is arbitrarily given a value of 1 so that the drug's affinity for all other sites can be expressed in relationship to its most potent site of action. The actual affinity in nanomolar concentration for its most potent site of action for each of the drugs listed above are as follows: aripiprazole D<sub>2</sub> (0.34), clozapine M<sub>1</sub> (1.9), haloperidol D<sub>2</sub> (0.7), olanzapine M<sub>1</sub> (1.9), quetiapine α<sub>1</sub> (7), risperidone α<sub>1</sub> (0.7), ziprasidone 5-HT<sub>2A</sub> (0.7).

\*Partial agonist at D<sub>2</sub> receptor where others in this table are full antagonists.

Relative binding affinity=binding affinity relative to the most potent site of action. D=dopamine; 5-HT=serotonin; H=histamine; M=muscarine.

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TABLE 10

RELATIVE BINDING AFFINITY OF SPECIFIC ANTIDEPRESSANTS TO SPECIFIC NEUROTRANSPORTERS AND NEURORECEPTORS<sup>\*5,47,80</sup>

Tertiary Amine TCAs	SET	NET	DAT	H <sub>1</sub>	M <sub>1</sub>	α <sub>1</sub>	α <sub>2</sub>	D <sub>2</sub>	5-HT <sub>2A</sub>
Amitriptyline	4	34	>1,000	1	16	25	827	910	27
Amoxapine	57	16	>1,000	24	970	49	>1,000	17	1
Chlorimipramine <sup>†</sup>	1	133	>1,000	113	133	138	>1,000	679	97
Doxepin	280	124	>1,000	1	350	100	>1,000	>1,000	105
Imipramine	1	26	>1,000	8	65	65	>1,000	>1,000	55
Trimipramine	552	>1,000	>1,000	1	88	88	>1,000	661	119
<b>Secondary Amine TCAs</b>									
Desipramine <sup>‡</sup>	21	1	>1,000	132	235	156	>1,000	>1,000	333
Maprotiline	>1,000	6	500	1	278	45	>1,000	172	60
Nortriptyline	4	1	261	2	34	14	575	277	10
Protriptyline <sup>‡</sup>	14	1	>1,000	18	18	92	>1,000	>1,000	47
<b>Selective Serotonin Reuptake Inhibitors</b>									
Citalopram	1	>1,000	>1,000	410	>1,000	>1,000	>1,000	NA	>1,000
Escitalopram	1	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000	NA	NA
Fluoxetine	1	293	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000	250
Fluvoxamine	1	584	>1,000	>1,000	>1,000	>1,000	>1,000	NA	>1,000
Paroxetine	1	320	>1,000	>1,000	860	>1,000	>1,000	>1,000	>1,000
Sertraline	1	>1,000	85	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000
<b>Selective Norepinephrine Reuptake Inhibitor</b>									
Reboxetine	8	1	>1,000	44	933	>1,000	NA	NA	875
<b>Dual Serotonin and Norepinephrine (SE<sub>≥</sub>NE) Reuptake Inhibitors</b>									
Duloxetine <sup>§</sup>	1	9.4	300	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000
Milnacipran	1	9	>1,000	>1,000	>1,000	>1,000	>1,000	NA	917
Venlafaxine <sup>§</sup>	1	30	93	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000

(cont. on page 56)

TABLE 10 (CONT.)

RELATIVE BINDING AFFINITY OF SPECIFIC ANTIDEPRESSANTS TO SPECIFIC NEUROTRANSPORTERS AND NEURORECEPTORS\*<sup>5,47,80</sup>

	SET	NET	DAT	H <sub>1</sub>	M <sub>1</sub>	α <sub>1</sub>	α <sub>2</sub>	D <sub>2</sub>	5-HT <sub>2A</sub>
<b>5-HT<sub>2A</sub> Inhibition and Weak Serotonin</b>									
Nefazodone	60	107	107	6	>1,000	8	>1,000	273	1
Trazodone	21	>1,000	929	45	>1,000	5	65	500	1
<b>Specific Histamine, Serotonin, and Norepinephrine Receptor Antagonist</b>									
Mirtazapine	>1,000	>1,000	>1,000	1	>1,000	>1,000	986	>1,000	115
<b>Dopamine and Norepinephrine (weak) Reuptake Inhibitor</b>									

The most potent site of action for a specific drug is arbitrarily given a value of 1 so that the drug's affinity for all other sites can be expressed in relationship to its most potent site of action. The actual affinity in nanomolar concentration for its most potent site of action for each of the drugs listed above are as follows: amitriptyline H (1), amoxapine 5-HT<sub>2</sub> (1), bupropion (526), citalopram SET (1.16), chlorimipramine SET (0.28), desipramine NET (0.83), doxepin H (0.24), duloxetine SET (0.8), fluoxetine SET (0.83), fluvoxamine SET (2.22), imipramine SET (1.41), maprotiline H<sub>1</sub> (2), milnacipran SET (9), mirtazapine H<sub>1</sub> (0.14), nefazodone 5HT<sub>2A</sub> (3.33), nortriptyline NET (4.35), paroxetine SET (0.13), protriptyline NET (1.41), reboxetine NET (7), sertraline SET (0.29), trazodone 5-HT<sub>2A</sub> (7.7), trimipramine H<sub>1</sub> (0.27), venlafaxine SET (82).

\*Relative binding affinity=binding affinity for most potent site of action.

† While chlorimipramine is a selective serotonin reuptake inhibitor, its principal active metabolite, desmethylchlorimipramine, is a selective norepinephrine reuptake inhibitor. Which action predominates is a function of the relative accumulation of these two compounds in a given patient.

‡ This drug is also a selective norepinephrine reuptake inhibitor.

§ Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology*. 2001;25(6):871-880

TCAs=tricyclic antidepressants; SET=serotonin transporter; NET=norepinephrine transporter; H=histamine; M=muscarine; D=dopamine; 5-HT=serotonin; SE=serotonin; NE=norepinephrine; NA=not applicable. Reproduced with permission. ©Preskorn.

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TABLE 11

RELATIVE BINDING AFFINITY OF SELECTED OLDER ANTIPSYCHOTICS FOR SPECIFIC NEURORECEPTORS\*<sup>51-55,80</sup>

Drug	D <sub>2</sub>	5-HT <sub>2A</sub>	α <sub>1</sub>	α <sub>2</sub>	H <sub>1</sub>	M <sub>1</sub>
Chlorpromazine	13	1	2	546	6	50
Cis-Thiothixene	1	289	24	444	13	>1,000
Fluphenazine	1	24	11	>1,000	26	>1,000
Loxapine	12	1	20	>1,000	4	331
Thioridazine	5	4	1	167	3	3

In this table, the most potent site of action for a specific drug is arbitrarily given a value of 1 so that the drug's affinity for all other sites can be expressed in relationship to its most potent site of action. The actual affinity in nanomolar concentration for its most potent site of action for each of the drugs listed above are as follows: chlorpromazine 5-HT<sub>2A</sub> (1.41), cis-thiothixene D<sub>2</sub> (0.45), fluphenazine D<sub>2</sub> (0.8), loxapine 5-HT<sub>2A</sub> (1.37), thioridazine α<sub>1</sub> (5).

\* Relative binding affinity=binding affinity relative to the most potent site of action.

D=dopamine; 5-HT=serotonin; H=histamine; M=muscarine.

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TABLE 12

FIVE REASONS FOR POLYPHARMACY<sup>59,81</sup>

1. To treat a concomitant disorder
2. To treat an intervening phase of the illness
3. To treat an adverse effect
4. To boost or augment the desired effect
5. To speed the onset of the desired effect

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TABLE 13

PARKINSON'S DISEASE AS A MODEL OF RATIONAL COPHARMACY<sup>59,81</sup>

Treatment	Effect
L-Dopa	Increase synthesis of central dopamine
L-Dopa + carbidopa (Sinemet)	Carbidopa inhibits peripheral decarboxylase to reduce the dose of L-dopa needed to increase synthesis of central dopamine (type*: pk)
L-Dopa/carbidopa + dopamine reuptake inhibitor (eg, bupropion, amantadine)	Second drug potentiates the effect of released central dopamine (type*: pk)
L-Dopa/cardibopa + L-deprenyl	L-deprenyl increases synthesis of central dopamine and blocks its degradation (type*: pk)

(cont. on page 57)

TABLE 13 (CONT.)

**PARKINSON'S DISEASE AS A MODEL OF RATIONAL COPHARMACY<sup>59,81</sup>**

Treatment	Effect
L-Dopa/carbidopa + bromocriptine	Bromocriptine and related D <sub>2</sub> agonists potentiate central dopamine agonism by addition of direct dopamine agonist (type*: pd)

\*Type of interaction: pk=pharmacokinetic; pd=pharmacodynamic.

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TABLE 14

**CRITERIA FOR RATIONAL COPHARMACY IN PSYCHIATRY<sup>35,59,81</sup>**

1. Knowledge that the combination has a positive effect on the pathophysiology or pathoetiology of the disorder
2. Convincing evidence that the combination is more effective, including more cost-effective, than monodrug therapy
3. The combination should not pose significantly greater safety or tolerability risks than monotherapy
  - Drugs should not have narrow therapeutic indices
  - Drugs should not have poor tolerability profiles
4. Drugs should not interact both pharmacokinetically and pharmacodynamically
5. Drugs should have mechanisms of action that are likely to interact in a way that augments the desired response
6. Drugs should have only one mechanism of action
7. Drugs should not have a broad-acting mechanism of action
8. Drugs should not have the same mechanism of action
9. Drugs should not have opposing mechanisms of action
10. Each drug should have simple metabolism
11. Each drug should have an intermediate half-life
12. Each drug should have linear pharmacokinetics

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TABLE 15

**THE HUMAN BRAIN<sup>89</sup>**

- |                               |                            |
|-------------------------------|----------------------------|
| • 10–20 billion cells         | • 2–17 receptor subtypes   |
| • 75 known neurotransmitters* | • Second messenger systems |
| • Enzymes                     | • Ion channels             |
- Transport mechanisms, storage and release

\* The number is likely to increase as more neurotransmitters are discovered through molecular biology.

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TABLE 16

**SUMMARY OF MAJOR PRINCIPLES TO AVOID ADVERSE DRUG-DRUG INTERACTIONS\***

- Be aware and follow good clinical practices
- Avoid multiple-target medications that affect nonessential targets
- Use logic rather than memorization or denial
- Use available literature and software
- When in doubt, start low and go slow
- Monitor for adverse outcome
- Anticipate and prevent by avoiding when possible:
  - highly potent inducers/inhibitor
  - drugs with a narrow therapeutic index
- When possible, choose low-risk perpetrators
- When possible, choose victims with multiple parallel pathways

\* Remember that the adverse effects of many psychiatric medications can mimic the illness being treated. Hence, patients may not be doing well because of their drug treatment rather than in spite of it.

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TABLE 17

**MAJOR PHARMACODYNAMIC DRUG-DRUG INTERACTIONS BASED ON MECHANISM OF ACTION<sup>80,94</sup>****Acetylcholine****Muscarinic Acetylcholine Receptor Antagonism**

- Mitigates and can even fully reverse the EPS caused by excessive D<sub>2</sub> blockade
- Can block the memory enhancing effects of cholinesterase inhibitors in dementing illnesses, such as Alzheimer's disease
- Decreases gastric emptying, thus decreasing the absorption of acetaminophen
- **Cholinesterase Inhibition:** Opposite consequences to muscarinic acetylcholine receptor antagonism. See above

**Biogenic Amine (effects on dopamine, norepinephrine, and serotonin)****Catechol-O-Methyltransferase Inhibition**

- Potentiate the effects of other drugs increasing the synaptic concentration of D, NE, and 5-HT syndrome. Could theoretically increase the likelihood and severity of hypertensive crisis and serotonin syndrome
- Antagonize the effects of drugs that block specific D, NE, and 5-HT receptors

**Monoamine Oxidase Inhibition**

- Potentiate the effects of other drugs increasing the synaptic concentration of D, NE, and 5-HT syndrome. Known to cause the hypertensive crisis and the serotonin syndrome when used in combination with drugs which have agonistic effects on central NE and 5-HT systems
- Augment and prolong the efficacy of dopamine agonists for the treatment of Parkinson's disease
- Can increase the likelihood and severity of dyskinesia, hyperactivity, and hyperkinesias, and psychosis and hyperactivity induced by dopamine agonists
- Antagonize the effects of drugs that block specific D, NE, and 5-HT receptors

(cont. on page 58)

TABLE 17 (CONT.)

**MAJOR PHARMACODYNAMIC DRUG-DRUG INTERACTIONS  
BASED ON MECHANISM OF ACTION<sup>80,94</sup>****Release**

- Can amplify the effects of other drugs increasing the synaptic concentration of D, NE, and 5-HT syndrome. Known to cause the hypertensive crisis and the 5-HT syndrome when used in combination with drugs, which have agonistic effects on central NE and 5-HT systems
- Augment and prolong the efficacy of D agonists for the treatment of Parkinson's disease
- Can increase the likelihood and severity of dyskinesia, hyperactivity, hyperkinesia, and psychosis induced by D agonists
- Antagonize the effects of drugs that block specific D, NE, and 5-HT receptors

**Dopamine (D)****Dopamine agonism (General)**

- Can ameliorate Parkinson's disease
- Can cause dyskinesia, hyperactivity, hyperkinesia, and psychosis

Above effects can be augmented by other D agonists and blocked by D antagonists

**D<sub>2</sub> Agonism**

- Can ameliorate Parkinson's disease
- Can cause dyskinesia, hyperactivity, hyperkinesia, and psychosis
- Can aggravate dyskinesias in conditions such as Huntington's disease

Above effects can be augmented by other D agonists and blocked by D antagonists

**Dopamine Uptake Inhibition**

- Can ameliorate Parkinson's disease and cause dyskinesia, hyperactivity, hyperkinesia, and psychosis

Above effects can be augmented by other dopamine agonists and blocked by D antagonists

**Dopa Decarboxylase Inhibition**

- Decrease the peripheral conversion of L-dopa to D and thus increase its availability to the brain increasing its net central D agonistic effects

**Selective D<sub>2</sub> Receptor Antagonism**

- Can cause EPS, including Parkinsonism
- Can aggravate Parkinson's disease
- Can reduce dyskinesias in conditions such as Huntington's disease and reduce psychosis seen in a number of other illnesses
- Can reverse hyperactivity and hyperkinesias caused by D agonists

**D<sub>2</sub> Receptor Partial Agonism**

- Reduced risk of EPS, including Parkinsonism
- Reduced risk of aggravating Parkinson's disease and bradykinesia seen in other dementing illnesses such as AD
- Could have variable effects on dyskinesias in conditions such as Huntington's disease
- Can reduce psychosis seen in a number of illnesses
- Should reduce the hyperactivity and hyperkinesias caused by D agonists

**Ethanol**

The CNS impairment caused by ethanol can be enhanced by a number of different mechanistic classes of drugs including:

- Drugs which promote GABA in the brain
- Drugs which block central H<sub>1</sub> receptors
- Opiates

**GABA****Barbiturates**

The CNS impairment caused by ethanol can be enhanced by a number of different mechanistic classes of drugs including:

- Other drugs which promote GABA in the brain
- Drugs which block central H<sub>1</sub> receptors
- Opiates, ethanol
- Barbiturate-like drugs (See barbiturates above)
- Benzodiazepine binding site agonism (See barbiturates above)
- Benzodiazepine-like drugs (See barbiturates above)
- GABA transaminase inhibition and stimulation of glutamic acid decarboxylase (See barbiturates above)
- Promotion of nonvesicular release of GABA (See barbiturates above)

**Histamine****Central Active H<sub>1</sub> Antagonism**

The sedation caused by central H<sub>1</sub> antagonism can be amplified by:

- Drugs which promote GABA in the brain
- Ethanol, opiates

**Ion Channel Inhibition**

There is a concern that effect of drugs which inhibit ion channel function may have additive or synergistic effects in terms of prolonging intracardiac conduction and/or causing seizures. These theoretical effects have not been formally tested due to the potential risk involved but have lead in some instances to class labeling warning against such combined use.

**Norepinephrine** **$\alpha_1$  Antagonism**

This mechanism can cause decreased peripheral arterial resistance leading to hypotension particularly orthostatic hypotension. Thus, neuropsychiatric medications with this mechanism of action can amplify the blood pressure lowering effects of a number of antihypertensive medications including  $\alpha_2$  agonists, angiotensin converting enzyme inhibitors,  $\beta$ -blockers, calcium channel inhibitors, and diuretics.

 **$\alpha_2$  Agonism**

This mechanism decreases central norepinephrine outflow and was initially used to treat hypertension. Rapid reversal of this effect either by abruptly stopping drugs such as clonidine or by administering an  $\alpha_2$  antagonist can cause clinically serious hypertensive rebound.

- Mirtazapine is an  $\alpha_2$ -adrenergic antagonist.
- By decreasing norepinephrine outflow,  $\alpha_2$ -adrenergic agonists would be expected to antagonize the effects of neuropsychiatric medications that block norepinephrine uptake pumps and MAOIs.

**Norepinephrine Uptake Pump Inhibition**

- The effect of these drugs would be reduced by  $\alpha_2$ -adrenergic agonists (eg, clonidine) and would be amplified/enhanced by  $\alpha_2$ -adrenergic antagonists (eg, mirtazapine).
- This mechanism can cause generally modest blood pressure elevations through enhancing sympathetic vascular tone. This effect would modestly antagonize the effects of a variety of blood pressure lowering agents.
- This mechanism can amplify the effect of MAOIs by increasing the duration of norepinephrine in the synaptic cleft while the MAOIs increase the intracytoplasmic stores of NE available for release when the adrenergic neurons fire.

(cont. on page 59)

TABLE 17 (CONT.)

**MAJOR PHARMACODYNAMIC DRUG-DRUG INTERACTIONS BASED ON MECHANISM OF ACTION<sup>80,94</sup>*****Norepinephrine and Serotonin (NE>SE) Uptake Pump Inhibition***

These drugs carry with them the potential for combined interactions associated with either of these mechanisms. See each section on each single mechanism in isolation. The relative magnitude of the interaction mediated by each mechanism would be a function of the concentration of the drug and thus the degree of specific uptake inhibition that is achieved.

***Dual Norepinephrine and Serotonin (NE>SE) Uptake Pump Inhibition Plus Other Actions***

These drugs would have the potential interactions mediated by each of the individual mechanisms. The relative magnitude of the interaction mediated by each mechanism would be a function of the concentration of the drug and thus the degree to which each mechanism is affected. Refer to tables on relative binding affinity and refer to each section on each mechanism for the potential interactions that could occur.

***Opiate Receptor Agonism***

The decreased CNS arousal particularly respiratory depression caused by opiates can be amplified by:

- Drugs which promote GABA in the brain
- Drugs which block central H<sub>1</sub> receptors
- Ethanol

***5-HT******5-HT<sub>1A</sub> Partial Agonism***

The pharmacology of these drugs is complicated. These receptors exist both presynaptically and postsynaptically. Presynaptically they are analogous to the  $\alpha_2$ -adrenergic receptor as a feedback mechanism. Postsynaptically, they serve an effector mechanism. In addition, the effect of these drugs is dependent on the intrasynaptic concentration of serotonin. At low concentrations, they act as a 5-HT<sub>1A</sub> agonist to diminish serotonin outflow. At high serotonin concentrations, they act as a 5-HT<sub>1A</sub> antagonist. Thus, they can theoretically interact in complex and even paradoxical ways with other serotonin active drugs. They can thus:

- Amplify the effects of serotonin uptake pump inhibitors in theory, and thus have been used as an augmenting strategy for antidepressant response but the only large clinical trial performed did not support this concept.

For the same reason, there is a theoretical risk of serotonin syndrome when combined with serotonin uptake pump inhibitors and/or MAOIs.

***5-HT<sub>1B/D</sub> Agonism***

There is a theoretical risk of serotonin syndrome when combined with other 5-HT agonists such as serotonin uptake pump inhibitors and MAOIs.

***5-HT<sub>2</sub> Receptor Antagonism***

5-HT agonism at this receptor may be responsible for the disruption of sleep that can be caused by serotonin uptake pump inhibitors. Trazodone blocks this receptor and is commonly used to treat the insomnia associated with serotonin uptake pump inhibitors.

***5-HT<sub>2A</sub> and D<sub>2</sub> Receptor Antagonism***

These drugs have the potential for interactions mediated by either of these mechanisms. See the comments under each of these mechanisms.

***5-HT<sub>2A</sub>, D<sub>2</sub>, and Multiple Other Receptor Antagonism***

These drugs have the potential for interactions mediated by all of these mechanisms.

See the comments under each relevant mechanism.

***Serotonin Uptake Inhibition***

The effects of these drugs can be substantially amplified by MAOIs to the point of causing fulminant and fatal serotonin syndromes. Serotonin syndrome is a theoretical risk when combined with 5-HT<sub>1A</sub> partial agonists and 5-HT<sub>1B/D</sub> agonists.

Lithium, by facilitating the neuronal release of serotonin, can enhance the 5-HT agonism produced by serotonin uptake pump inhibitors. Since serotonin is an inhibitory neurotransmitter for dopamine cell firing, this mechanism may account for the increased tremors that can occur with the combined use of lithium and a serotonin uptake pump inhibitor.

***Selective Serotonin Uptake Inhibition***

See comment under serotonin uptake inhibition

***Dual Serotonin and Norepinephrine (SE>NE) Uptake Pump Inhibition***

See comment under dual serotonin and norepinephrine uptake pump inhibition

EPS=extrapyramidal side effects; D=dopamine; NE=norepinephrine; 5-HT=serotonin; CNS=central nervous system; GABA= $\gamma$ -aminobutyric acid; H=histamine; MAOIs=monoamine oxidase inhibitors; SE=serotonin.

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TABLE 18

**POTENTIAL MECHANISMS UNDERLYING PHARMACOKINETIC DRUG-DRUG INTERACTIONS**

- Protein binding\*

- Phase I enzymes

CYPs and non CYPs

- Phase II enzymes

- ABC transporters

- Nuclear receptors

\* Although firmly entrenched in the minds of physicians, this mechanism rarely mediates clinically significant drug-drug interactions as explained in the text.

CYP=cytochrome P450; ABC=adenosine triphosphate-binding cassette.

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TABLE 19

**DRUGS CATEGORIZED AS SPECIFIC CYP ENZYME SUBSTRATES, INHIBITORS, OR INDUCERS TO PERMIT PREDICTION OF CYP MEDIATED DRUG-DRUG INTERACTIONS<sup>35</sup>****CYP 1A2**

<u>Substrates</u>		<u>Inhibitors</u>	<u>Inducers</u>
Bortezomib (Velcade)	Haloperidol (Haldol)	Amiodarone (Cordarone, Pacerone)	Broccoli
Clozapine (Clozaril)	Imipramine (Tofranil)	Cimetidine (Tagamet)	Brussel sprouts
Cyclobenzaprine (Cyclobenz, Flexeril)	Olanzapine (Zyprexa)	Fluoroquinolones (Various drugs)	Chargrilled meat
Cinacalcet (Sensipar)	Ramelteon (Rozerem)	Fluvoxamine (Luvox) <sup>†</sup>	Modafinil (Provigil)
Duloxetine (Cymbalta)	Riluzole (Rilutek)	Methoxsalen (Oxsoalene-Ultra, Uvadex)	Tobacco
Fluvoxamine (Luvox)	Tacrine (Cognex)	Ticlopidine (Ticlid)	
	Zolmitriptan (Zomig)		

**CYP 2B6**

<u>Substrates</u>		<u>Inhibitors</u>	<u>Inducers</u>
Bupropion (Wellbutrin, Zyban)	Methadone (Dolophine)	Thiotepa (Thioplex)	Phenobarbital (Phenob)
Efavirenz (Sustiva)		Ticlopidine (Ticlid)	Rifampin (Rifadin, Rifamate, Rimactane)

**CYP 2C9**

<u>Substrates</u>	<u>Inhibitors</u>	<u>Inhibitors</u>	<u>Inducers</u>
Amitriptyline (Elavil, Endep)	Amiodarone (Cordarone, Pacerone)	Isoniazid (Rifater, Nydrazid)	Rifampin (Rifadin, Rimactane, Rifamate)
Bortezomib (Velcade)	Fluconazole (Diflucan)	Sulfamethoxazole (Bactrim, Bethaprim, Cotrim, Septra, Sulfatrim, Trimeth-Sulfa, Gantanol)	Secobarbital (Seconal, Tuinal)
Fluoxetine (Prozac, Sarafem)	Fluoxetine (Prozac) <sup>†</sup>	Sulfaphenazole (Clinalfa)	
Phenytoin (Dilantin)	Fluvastatin (Lescol)	Teniposide (Vumon)	
S-warfarin (Coumadin)	Fluvoxamine (Luvox)	Zafirlukast (Accolate)	

**CYP 2C19**

<u>Substrates- Antiepileptics</u>	<u>Substrates- Other</u>	<u>Inhibitors</u>	<u>Inducers</u>
Phenobarbitone (ADCO-phenobarbitone Vitalet Elixir)	Amitriptyline (Elavil, Endep)	Cimetidine (Tagamet)	Carbamazepine (Carbatrol, Epital, Tegretol)
Phenytoin (Dilantin)	Bortezomib (Velcade)	Felbamate (Felbatol)	Norethindrone (Brevicon, Norinyl, Ortho-Novum)
Primidone (Mysoline)	Citalopram (Celexa)	Fluoxetine (Prozac, Sarafem) <sup>†</sup>	NOT pentobarbital (Nembutal, Pentobarb)
R-mephobarbital (Mebaral)	Clomipramine (Anafranil)	Fluvoxamine (Luvox) <sup>†</sup>	
S-mephentoin (Mesantoin)	Diazepam (Valium)	Indomethacin (Indocin)	Prednisone (Deltasone, Liquid Pred, Orasone, Sterapred)
Omeprazole	Imipramine (Tofranil)	Ketoconazole (Nizoral)	Rifampin (Rifadin, Rifamate, Rimactone)
Lansoprazole	Nelfinavir (Mebaral)	Lansoprazole (Prevacid)	
Pantoprazole	Nilutamide (Niladron)	Omeprazole (Prilosec)	
	Moclobemide (Manerx, Auroix)	Probenicid (Colbenemid, Probene)	
	Rosuvastatin (Crestor)	Ticlopidine (Ticlid)	
		Topiramate (Topamax)	

**CYP 2D6**

<u>Substrates- Antidepressants</u>	<u>Substrates- Antidepressants</u>	<u>Inhibitors</u>	<u>Inhibitors</u>
Amitriptyline (Elavil, Endep)	Fluvoxamine (Luvox)	Amiodarone (Cordarone, Pacerone)	Reduced-haloperidol (metabolite)
Atomoxetine (Strattera)	Imipramine (Tofranil)	Bupropion (Wellbutrin, Zyban) <sup>†</sup>	Levomopromazine (Various different drugs)
Clomipramine (Anafranil)	Nortriptyline (Pamelor)	Celecoxib (Celebrex)	Metoclopramide (Metoclopram, Reglan)
Duloxetine (Cymbalta)	Paroxetine (Paxil, Asimia)	Chlorpheniramine (Chlor-Trimeton, Efidac)	Methadone (Dolphine)
Desipramine (Norpramin)	Venlafaxine (Effexor)	Chlorpromazine (Thorazine)	Mibefradil (Posicor)
Fluoxetine (Prozac, Sarafem)		Cimetidine (Tagamet)	Moclobemide (Manerx, Auroix)
		Citalopram (Celexa) <sup>†</sup>	Paroxetine (Paxil, Asimia)

(cont. on page 61)

<b>Substrates- Antidepressants</b>	<b>Substrates- Antidepressants</b>	<b>Inhibitors</b>	<b>Inhibitors</b>
		Clomipramine (Anafranil)	Quinidine (Quinaglute, Cardioquin, Quinidex)
		Duloxetine (Cymbalta) <sup>†</sup>	Sertraline (Zoloft) <sup>†</sup>
		Escitalopram (Lexapro) <sup>†</sup>	Terbinafine (Lamisil)
		Fluoxetine (Prozac, Sarafem) <sup>†</sup>	

<b>Substrates- Antipsychotics</b>	<b>Substrates- Antipsychotics</b>
Aripiprazole (Abilify)	Perphenazine (Trilafon)
Chlorpromazine (Thorazine)	Risperidone (Risperdal)
Haloperidol (Haldol)	Thioridazine (Mellaril)
<b>Substrates- Other</b>	<b>Substrates- Other</b>
Bortezomib (Velcade)	Galantamine (Razadyne)
Chlorpheniramine Chlor-Trimeton, Efidac)	Thioridazine (Mellaril)
Cinacalcet (Sensipar)	Perphenazine (Trilafon)
Codeine	Risperidone (Risperdal)
Dexfenfluramine (Redux)	Minaprine (Cantor)
Donepezil (Aricept)	Palonosetron (Aloxi)

**CYP 2E1**

<b>Substrates</b>	<b>Substrates</b>	<b>Inhibitors</b>	<b>Inhibitors</b>
Acetaminophen (Tylenol, etc)	Eszopiclone (Lunesta)	Disulfiram (Antabuse)	Isoniazid (Nydrazid, Rifater)
Chlorzoxazone (Paraflex, Parafon Forte)		Ethanol (Dehydrated alcohol)	

**CYP 3A4, 3A5, 3A7**

<b>Substrates- Benzodiazepines</b>	<b>Substrates- Antihistamines</b>	<b>Inhibitors</b>	<b>Inhibitors</b>
Alprazolam (Xanax)	Chlorpheniramine (Chlor-Trimeton, Efidac)	Amiodarone (Cordarone, Pacerone)	Fosamprenavir (Lexiva)
Diazepam (eg, Valium)	Clarithromycin	Atazanavir (Reyataz)	Gestodene (Various different drugs)
Midazolam (Versed)	Cyclosporine	NOT azithromycin (Zithromax)	Grapefruit Juice
Triazolam (Halcion)	Erythromycin	Cimetidine (Tagamet)	Indinavir (Crixivan)
	Ramelteon	Clarithromycin (Biaxin)	Itraconazole (Sporanox)
<b>Substrates-Other</b>	<b>Substrates-Other</b>	<b>Inhibitors</b>	<b>Inhibitors</b>
Alfentanil (Alfenta)	Odanestron	Delaviridine (Rescriptor)	Ketoconazole (Nizoral)
		Diltiazem (Cartia, Cardizem, Dilacor, Diltiazem, Taztia, Tiamate, Tiazac)	Nefazodone (Serzone) <sup>†</sup>
Aripiprazole (Abilify)	Pimozide (Orap)	Erythromycin (Emgel)	Nelfinavir (Viracept)
Buspirone (Buspar)	Quetiapine (Seroquel)	Fluconazole (Diflucan)	Norfloxacin (Chibroxin, Noroxin)
Codeine-N-demethylation	Trazodone (Desrel)	Fluvoxamine (Luvox) <sup>†</sup>	Norfluoxetine (metabolite) <sup>†</sup>
Eplerenone (Inspra)	Zaleplon (Sonata)		
Fentanyl (Aactiq, Duragesic, Sublimaze)	Ziprasidone (Geodon) <sup>‡</sup>		
Haloperidol (Haldol)	Zolpidem (Ambien)		
	Dextromethorphan (Benlyn DM, Delsym, Touro DM, Tussi Org)		

**Inducers****Barbiturates**

Carbamazepine (Carbatrol, Epital, Tegretol)	Phenytoin (Dilanten)
Efavirenz (Sustiva)	Rifabutin (Mycobutin)
Modafinil (Provigil)	Rifampin (Rifadin, Rifamate, Rimactane)
Nevirapine (Viramune)	St. John's Wort (Hypericum perforatum)
Phenobarbital (Phenob)	Tipranavir (Aptivus)

<sup>†</sup>Degree of inhibition is dose-dependant for this drug and most inhibitors in this table. Refer to Table 2 for relative magnitude of inhibition produced by usually effective antidepressant dose.

<sup>‡</sup>Ziprasidone is principally cleared by aldehyde oxidase, which is not a CYP enzyme. CYP3A4 accounts for approximately 1/3 of ziprasidone clearance.

Modified by the authors for this publication.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 13, No 4. 2006.

**TABLE 20**  
**LIMITATIONS OF CURRENT SOFTWARE PACKAGES<sup>107-111</sup>**

- May not be mechanism based
- Generally only a binary system (ie, Drug A affects Drug B)
- An alert rather than an information system
- Limited knowledge base
- Generally either PD or PK but not the interaction of PD and PK
- Little reference base in the literature

PD=pharmacodynamic; PK=pharmacokinetic.  
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**TABLE 21**  
**REPORTING ADVERSE DRUG REACTIONS<sup>114,115</sup>**

MedWatch: 1-800-FDA-1088 Fax: 1-800-FDA-0178  
Report online at: [www.fda.gov/medwatch](http://www.fda.gov/medwatch)  
Practitioner reporting online at: [www.usp.org](http://www.usp.org)

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 13, No 4. 2006.

## APPENDICES

### APPENDIX I WEB SITES<sup>35,59,102-106</sup>

While there are a large number of unreferenced Web sites available on the Internet, all of the following contain direct references or links to peer-reviewed medical literature.

<u>Description</u>	<u>URL</u>
Psychiatric Drug Interaction	<a href="http://www.preskorn.com">www.preskorn.com</a>
Cytochrome P450 Interactions	<a href="http://medicine.iupui.edu/flockhart/">http://medicine.iupui.edu/flockhart/</a>
Herbal Interactions	<a href="http://www.personalhealthzone.com/herbsafety.html">www.personalhealthzone.com/herbsafety.html</a>
HIV Drug Interactions	<a href="http://www.hiv-druginteractions.org/">www.hiv-druginteractions.org/</a>
HIV Drug Interactions	<a href="http://www.projinf.org/fs/drugin.html">www.projinf.org/fs/drugin.html</a>
Grapefruit Juice – Drug Interactions	<a href="http://www.powernetdesign.com/grapefriut/">www.powernetdesign.com/grapefriut/</a>
FDA Food and Drug Interactions	<a href="http://vm.cfsan.fda.gov/~lrd/fdinter.html">http://vm.cfsan.fda.gov/~lrd/fdinter.html</a>

HIV=human immunodeficiency virus; FDA=Food and Drug Administration.

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### APPENDIX II CURRENT DRUG DRUG INTERACTIONS SOFTWARE PACKAGES<sup>107-111</sup>

#### Drug Facts and Comparisons

Epocrates  
Hansten's  
Mhc.com/Cytochromes  
Micromedex

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## **NOTE:**

**This Educational Review is also available as a Clinical Handbook. Please see page 89.**

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