ABSTRACT

Drug-drug interactions (DDIs) are a concern for the prescriber because they have the potential for causing untoward outcomes for everyone involved: morbidity 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 ≥5 prescription medications in the week preceding the survey. Patients on psychiatric medications, such as antidepressants, are on more medication than patients not on psychiatric medications. Prescribers should appreciate that medications interact not on the basis of their therapeutic use, but on the basis of their pharmacodynamics and pharmacokinetics. For this reason, the prescriber of psychiatric medications must consider all of the medications the patient is taking. Similar to the 2006 version, this educational review focuses on neuropsychiatric medications but also covers all other drugs to the extent that they interact with psychiatric medications. It emphasizes the role of pharmacologic principles to guide the safe and effective use of multiple medications when such use is necessary. Consistent with these principles, this review presents tables outlining major pharmacodynamic and pharmacokinetic mechanisms mediating DDIs relevant to the patient on psychiatric medications.

FOCUS POINTS

- Patients with psychiatric disease are at increased risk relative to other age-matched patients for being on multiple medications and complex regimens, which makes them particularly vulnerable to drug interactions.
- Prescribers should appreciate that psychiatric medications do not interact principally on the basis of their therapeutic use but instead on the basis of their pharmacokinetic and pharmacodynamic properties.
- A rational and informed approach to drug interactions, based on pharmacokinetic and pharmacodynamic knowledge, can reduce the chance of adverse effects and improve patient outcomes.

INTRODUCTION

"Doctors pour drugs of which they know little, to cure diseases of which they know less, into patients of whom they know nothing." - Voltaire

"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." - Sir William Osler

"The true polypharmacy is the skilful combination of remedies." - Sir William Osler

The above quotes by Voltaire¹ and Osler² 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 that needed knowledge and skill. 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, particularly 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 which can be fatal. This syndrome can occur when a serotonin uptake pump inhibitor is used in combination with a monoamine oxidase inhibitor (MAOI).3

“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.

WHY A REVIEW ON PSYCHIATRIC MEDICATIONS AND DDIs?

There are two basic reasons for this review about psychiatric medications and DDIs. First, many patients are on psychiatric medications and the percentage has been continuously increasing over the past 2 decades. Second, patients on psychiatric medications have an increased likelihood of being on more complex medication regimens compared to those not on psychiatric medications and, hence, are at increased risk of experiencing a DDI.

In 2005, antidepressants surpassed antihypertensives to become the most commonly prescribed class of medications such that one out of 10 Americans ≥6 years of age was on an antidepressant.4 That translates into 27 million Americans in 2005. Of these, 38% were on at least one other psychotropic: 24% on an anxiolytic or hypnotic, 9% on an antipsychotic, 6% on a mood stabilizer, and 6% on a stimulant, with a number of these patients being on ≥2 psychotropics.5 There is every indication that the use of psychiatric medication has continued to increase since 2005 such that more than one of 10 Americans are likely to be on at least one antidepressant as of 2010. The majority of the patients receiving psychiatric medications are being treated by their primary care physician (PCP) rather than by a psychiatrist. PCPs commonly have only 4–8 weeks of psychiatric training during medical school and limited, if any, formal training in clinical psychopharmacology or psychiatry during their postgraduate residency training. These facts alone underscore the need for such a review, but that need is further amplified by the fact that patients on psychiatric medications such as antidepressants are more likely to be on other medications.

HOW DO DDIs PRESENT AND HOW IMPORTANT ARE THEY?

DDIs can mimic virtually any clinical presentation imaginable from the catastrophic to the everyday 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 caused by the drugs the patient is taking, and the clinical outcome the prescriber 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,5-7 seizures,8 cardiac rhythm disturbances,9,10 serotonin syndrome,11 malignant hypertension,12 neuroleptic malignant syndrome,13 and delirium.14,15
2. Poor tolerability (ie, patient is “sensitive” to adverse drug effect)9,10,16-20
3. Lack of efficacy (ie, patient is “resistant” to beneficial drug effect).21
4. Symptoms that mimic and hence lead to misdiagnosis of a new disease.22-24
5. The apparent worsening of the disease being treated.16-18
6. Withdrawal symptoms or drug-seeking behavior on the part of the patient.25

Preskorn26 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. The goal of the case reports is to aid prescribers in recognizing DDIs when they occur and to understand their

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clinical significance by giving them case-based examples. The interested reader can access those case reports at www.preskorn.com under the section, “Columns, Case Studies.”

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 conducted in Denmark,27-29 England,30,31 Sweden,32 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. More importantly, the vast majority of the individuals are on unique combinations of medications (ie, one specific combination for each individual in populations numbering 5,000–10,000 individuals).

The second comment is the issue of what constitutes clinical relevance, which has been discussed at length.33,34 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, Ray and colleagues35 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 study20 took poor tolerability leading to the discontinuation of the victim drug as the clinically significant outcome. This study found that the co-prescription of risperidone and a substantial CYP2D6 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 CYP2D6 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 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 learning more about this topic is referred to other references,33,34 which address the topic of the clinical relevance of DDIs from a population perspective in greater detail.

**GOAL OF THIS REVIEW**

One goal 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 review is not intended to be comprehensive nor 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 review, 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). Thus, this review is intended to provide an introduction to the topic and to serve as a gateway to ready sources of additional information via the Internet.

In fact, both authors maintain Web sites relevant to DDIs. Flockhart’s Web site36 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. As mentioned earlier, Preskorn’s Web site26 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.26 The authors will refer to their own 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 review has been published.

Beyond the inevitability that all print material will become dated, this review 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).37 For this reason, the authors acknowledge the limitations inherent in focusing on a therapeutic class—even one as broad as psychiatric or neuropsychiatric medications. In fact, the authors will reclassify the drugs covered in this article into functional classes based on their pharmacodynamics and pharmacokinetics, such as CYP enzyme substrates, inducers, and inhibitors. The reason for taking this approach is that those are the mechanisms that underlie DDIs. For this same reason, the authors will also address the effects of psychiatric medications on nonpsychiatric medications, and vice versa, where appropriate.
With these caveats, this educational review will focus on neuropsychiatric medications. It will review the scope of the problem and discuss strategies and approaches to avoiding untoward and unintended DDIs. Summary figures embedded in the review and tables at the end of the article will highlight major DDIs involving psychiatric medications.

**CHANGES SINCE 2006**

The first edition of this review was published in early 2004 and a second edition in 2006. The number of approved new drugs (ie, new molecular entities as opposed to generic versions of existing drugs) was 26 in 2006, 52 in 2007, and 45 in 2008 for a total of 123 new drugs over that 3-year span (156 weeks), or one new drug entering the market virtually every week. The number of new drugs approved in 2009 is not being mentioned because the year is not yet completed.

A “new molecular entity” does not include the approval of specific enantiomers, active metabolites, reformulations, or generic versions of previously marketed drugs. Such products may be either important advances or of minimal added value, depending on the specific products. An example of the former is fexofenadine because in contrast to the original drug, terfenadine, it is not susceptible to a clinically important and potentially fatal DDI when co-administered with a potent CYP3A inhibitor.

Of the 123 new drugs approved over the last 3 years only two of these were approved for primary psychiatric indications, asenapine (Saphris) and iloperidone (Fanapt). The fact that there were only two new molecular entities approved for a primary psychiatric indication over the last 4 years is an indication of the substantial challenges inherent in developing novel psychiatric medications. While that topic is interesting in its own right, the discussion of the reasons is beyond the scope of this article.

In addition to asenapine and iloperidone, there were an additional five central nervous system (CNS) drugs approved for either a neurologic indication or smoking cessation. The latter refers to varenicline (Chantix), which will be discussed at some length in this article because a sizable percentage of patients on risperidone and venlafaxine are unable to convert the parent drug into its active metabolite, paliperidone and desvenlafaxine, respectively.

In addition to these new molecular entities, two active metabolites of previously marketed drugs were approved: paliperidone, the active metabolite of risperidone, and desvenlafaxine, the active metabolite of venlafaxine. Of interest, both are produced by oxidative metabolism mediated by CYP2D6. There are many variants of the CYP2D6 gene. Some of these variants result in no functional activity of the enzyme and some result in reduced activity compared to the “wild type” enzyme. Individuals with no activity are called CYP2D6 “poor” metabolizers (PMs) whereas those with reduced activity are called “intermediate” metabolizers (IMs). Most individuals have normal activity and are called “extensive” metabolizers (EMs). There are also individuals who have more than one copy of the CYP2D6 wild type gene and hence have greater ability to metabolize drugs via this enzyme and hence are call “ultrarapid” metabolizers (UMs).

However, the frequency of these four genotypes varies depending on the ethnicity of the population being studied. Figure 1 shows a frequency distribution curve for UMs, EMs, IMs, and PMs in a Caucasian population and the relationship to genotype. Up to 10% of Caucasians, particularly those from northern Europe, are PMs, whereas this percentage is only ≤1% in Chinese populations. Conversely, Asians have an increased likelihood of being IMs compared to Caucasians. Only 1% to 2% of Caucasians and Asians are UMs in contrast to 20% of individuals from northern Africa. For this reason, with drugs like risperidone and venlafaxine, there can be considerable variability in the pharmacokinetics and clinical effects amongst individuals in these different populations.

In addition, there are numerous drugs which can substantially inhibit CYP2D6 activity and hence can convert genetically CYP2D6 EMs into functional CYP2D6 PMs. These drugs include several antidepressants, including bupropion, fluoxetine, and paroxetine (Table 1). Fluoxetine and paroxetine at 40 mg/day will phenocvert 95% of genotypic CYP2D6 EMs into functional CYP2D6 PMs. Thus, both genetics and concomitant drug administration (ie, a DDI) can result in a sizable percentage of patients on risperidone and venlafaxine being unable to convert the parent drug into its active metabolite, paliperidone and desvenlafaxine, respectively.

There is some evidence that risperidone more than 9-hydroxy-risperidone (ie, paliperidone) may be associated with extrapyramidal side effects in individuals who are deficient in CYP2D6 activity due either to genetics or concomitant drug administration.  

![FIGURE 1](image_url)

**FIGURE 1**

**GENETICS OF CYP 2D6 METABOLIZING EFFECTS ON NORTRIPTYLINE**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenytoin frequency (Caucasian)</th>
<th>Ultrarapid metabolizers</th>
<th>Extensive metabolizers</th>
<th>Intermediate metabolizers</th>
<th>Poor metabolizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMs</td>
<td>5%–10%</td>
<td>95%–10%</td>
<td>5%–10%</td>
<td>10%–15%</td>
<td>5%–10%</td>
</tr>
<tr>
<td>EMs</td>
<td>95%–10%</td>
<td>95%–10%</td>
<td>10%–15%</td>
<td>5%–10%</td>
<td>5%–10%</td>
</tr>
<tr>
<td>PMs</td>
<td>10%–15%</td>
<td>10%–15%</td>
<td>5%–10%</td>
<td>5%–10%</td>
<td>5%–10%</td>
</tr>
</tbody>
</table>

Nortriptyline dose requirement (mg/day)

- >250–500 mg/day
- 150–300 mg/day
- 100–150 mg/day
- 50–100 mg/day
- 0–50 mg/day

MR=metabolic ratio of parent debrisoquine ÷ metabolic OH-debrisoquine.

There is also evidence that CYP2D6 activity is a critical factor in determining the antidepressant efficacy of desvenlafaxine. Based on a secondary analysis of the venlafaxine registration trials, patients who were CYP2D6 EMs experienced robust antidepressant efficacy when treated with venlafaxine, whereas there was no evidence of antidepressant efficacy based on response or remission rates between CYP2D6 PM patients treated with venlafaxine compared to patients treated with placebo.49

The results of these studies raise the possibility that the efficacy of venlafaxine and the tolerability of risperidone may be principally determined by desvenlafaxine and paliperidone, respectively. If that is the case, the metabolite would have an advantage over the parent drug in part because of the absence of susceptibility to genetically determined or drug-induced CYP2D6 activity. However, there are other possible explanations for these observations, including the possibility that CYP2D6 PM compared to EM patients have a more treatment-resistant form of refractory major depressive disorder (MDD) regardless of the specific antidepressant administered.

This article next focuses on the novel psychiatric medications approved in the last 4 years: asenapine, iloperidone, milnacipran, and varenicline, from the perspective of DDIs.40

Asenapine

Asenapine (Saphris) is an atypical antipsychotic which is indicated for acute treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults. As with virtually all newly marketed drugs, the risk of using asenapine in combination with other drugs has not been extensively evaluated. Hence, guidance in this area is cautious and guided principally by the known pharmacodynamics and pharmacokinetics of asenapine. The following is a summary of that guidance.

Like virtually all other atypical antipsychotics except aripiprazole, asenapine has greater binding affinity for the serotonin or 5-hydroxytryptamine (5-HT)2A versus the dopamine (D)1 receptor (Table 2).40,41 However, asenapine has comparable binding affinity for the 5-HT2C and the α1 adrenergic receptor and thus might cause orthostatic hypotension if the dose is escalated too rapidly, particularly early in treatment. In addition, it could accentuate the blood pressure-lowering effects of various types of antihypertensive medications, a pharmacodynamically mediated DDI. Hence, asenapine should be used cautiously in combination with other drugs that can induce hypotension as well as with drugs that can cause bradycardia or respiratory or CNS depression.

A formal QTc study of the effects of asenapine (5, 10, 15, and 20 mg/day) was conducted in 151 clinically stable individuals with schizophrenia. It was found that asenapine was associated with increases in the QTc interval ranging from 2–5 msec.42 Prolongations of this magnitude are not clinically meaningful. In addition, no individual in this study experienced QTc prolongation >60 msec nor a QTc >500 msec, the threshold above which the risk of torsades de pointes arrhythmia increases dramatically. There was also no QTc safety signal in the overall asenapine database. Despite these facts, the package insert warns against the use of asenapine in combination with other drugs known to prolong the QTc including Class IA antiarrhythmics (eg, quinidine, procainamide) or Class III antiarrhythmics (eg, amiodarone, sotalol), and an antipsychotic known to prolong the QTc (eg, chlorpromazine, thioridazine, ziprasidone).

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism predominantly mediated by CYP1A2. Hence, the potential effects of specific inhibitors and inducers of UGT1A4 and also several CYP enzymes on the clearance of a single 5 mg dose of asenapine was studied in normal volunteers during its development. Specifically, these studies involved: fluvoxamine (a substantial CYP 1A2 inhibitor) at a dose of 25 mg BID for 8 days, paroxetine (a substantial CYP2D6 inhibitor) at a dose of 20 mg QD for 9 days), imipramine (a weak CYP1A2, 2C19, and 3A4 inhibitor at a single dose of 75 mg, cimetidine (a weak CYP3A4, 2D6, and 1A2 inhibitor) at a dose of 800 mg BID for 8 days, valproate (a UGT1A2 inhibitor) at a dose of 500 mg BID for 9 days, and carbamazepine (a CYP 3A4 inducer) at a dose of 400 mg BID. Co-administration of fluvoxamine and carbamazepine in these studies produced a 29% increase and a 16% decrease in the area under curve (AUC) of asenapine, respectively. The other drugs produced smaller changes in the AUC of asenapine. Based on these studies, no dose adjustment of asenapine is used with drugs which are inhibitors of any of these enzymes except of CYP1A2.

Since CYP1A2 inhibition is proportional to the dose of fluvoxamine, and since the dose of fluvoxamine used in the above mentioned study was small relative to its usual therapeutic dose of fluvoxamine, caution is advised when dosing asenapine in the presence of fluvoxamine and other CYP 1A2 inhibitors. However, smoking does not appear to affect the clearance of asenapine based on population pharmacokinetic analysis of individuals who were and were not smokers in its clinical trial database and on a formal pharmacokinetic cross-over study in smokers.

Based on in vitro studies, asenapine is a weak CYP 2D6 inhibitor.40,41 The effect of asenapine on this CYP enzyme was further tested in three normal volunteer studies including the above mentioned paroxetine and imipramine studies plus a study using dextromethorphan as the CYP2D6 probe drug. Co-administration of a single 5 mg dose of asenapine produced a 2-fold increase in the AUC of paroxetine but did not affect the AUC of desipramine, the major metabolite of imipramine and a model CYP2D6 substrate. In a third study, the relative effects of co-administration of asenapine, 5 mg BID versus paroxetine 20 mg/day, on the CYP2D6-mediated conversion of dextromethorphan (DM) to its major metabolite, dextrorphan (DX), were tested. Asenapine co-administration decreased the DX/DM ratio to 0.43, whereas paroxetine co-administration
decreased this ratio to 0.032, consistent with the known substantial in vivo CYP2D6 inhibition produced by paroxetine (Table 1). Based on these studies, asenapine and/or a metabolite of asenapine may enhance the known inhibitory effects of paroxetine on its own metabolism. Parenthetically, CYP2D6 preferentially mediates the metabolism of paroxetine but is quickly inhibited as the paroxetine levels increase (ie, autoinhibition of paroxetine metabolism). Based on these results, asenapine should be co-administered cautiously with drugs that are either substrates and/or inhibitors of CYP2D6.

Iloperidone

Iloperidone (Fanapt) is an atypical antipsychotic which is indicated for the acute treatment of schizophrenia.

As with virtually all newly marketed drugs, the risk of using iloperidone in combination with other drugs has not been extensively evaluated. Hence, guidance in this area is based principally on the known pharmacodynamics and pharmacokinetics of iloperidone. The following is a summary of that guidance.

Like virtually all other atypical antipsychotics with the exception of aripiprazole, iloperidone has a greater binding affinity for the 5-HT2A versus the D2 receptor (Table 2). However, iloperidone also has substantial binding affinity for α1 adrenergic receptors and thus can cause orthostatic hypotension if the dose is elevated too quickly. In addition, it can potentiate the blood pressure-lowering effects of various types of antihypertensive medications, a pharmacodynamically mediated DDI. In addition, iloperidone can cause QTc prolongation which could theoretically be accentuated by co-administration with other drugs which are known to lengthen the QTc, another type of pharmacodynamic DDI. For this reason, caution is recommended when using iloperidone in combination with other drugs known to be capable of prolonging the QTc.

In addition to the above pharmacodynamic DDIs, iloperidone is also susceptible to CYP enzyme-mediated pharmacokinetic DDIs because it is metabolized approximately equally by CYP2D6 and CYP3A. When co-administered with a substantial CYP2D6 and 3A inhibitor (eg, paroxetine and ketoconazole, respectively), plasma concentrations of iloperidone can double and produce further prolongation of the QTc, on average, 19 msec prolongation. For these reasons, the dose of iloperidone should be reduced by 50% in such situations.

Although there are no formal studies, one would expect that potentially clinically meaningful decreases in iloperidone plasma concentration would occur if it were co-administered with a CYP3A inducer (eg, carbamazepine) such that a dose increase might be needed.

Milnacipran

Milnacipran (Savella) is a selective serotonin-norepinephrine reuptake inhibitor approved for the treatment of fibromyalgia. Pharmacodynamically, milnacipran would be expected to have the same interactions as with selective serotonin reuptake inhibitors (SSRIs) and other serotonin norepinephrine reuptake inhibitors (SNRIs): serotonin syndrome and hypertensive crisis when co-prescribed with MAOIs due to its ability to block serotonin and norepinephrine uptake, respectively.

However, it is not anticipated to be at risk for pharmacokinetically mediated DDIs for the following reasons. It has a high oral bioavailability (ie, 85% to 90%) and is not affected by being taken with or without food. It is predominantly (55%) excreted unchanged in the urine. Plasma protein binding is approximately 13%. Based on in vitro studies, milnacipran is not metabolized at clinically relevant concentrations by CYP enzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4; and does not inhibit human CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4; nor does it induce human CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4.

Based on in vivo studies, co-administration of milnacipran 100 mg/day and carbamazepine 200 mg BID did not produce clinically significant changes in the pharmacokinetics of milnacipran or carbamazepine and its epoxide metabolite. Co-administration of milnacipran 200 mg/day and digoxin 0.2 mg/day for multiple days did not alter the pharmacokinetics of either drug in healthy volunteers. An abrupt switch from fluoxetine 20 mg once a day to milnacipran 100 mg/day without a washout period did not affect the pharmacokinetics of milnacipran, which is noteworthy because fluoxetine is a long-lived and strong inhibitor of CYP2D6 and a moderate inhibitor of CYP2C19. The pharmacokinetics of milnacipran and warfarin were not altered by co-administration. Co-administration of milnacipran did not alter the pharmacokinetics of either lithium or lorazepam. A switch from clomipramine 75 mg once a day to milnacipran 100 mg/day without a washout period did not lead to clinically significant changes in the pharmacokinetics of milnacipran but there was an increase in specific adverse events (eg, euphoria and postural hypotension), leading to the recommendation to increase the monitoring of patients when such a treatment switch is initiated.

Varenicline

Varenicline (Chantix) is a high-affinity and selective α4 β2 nicotinic agonist approved as an aid in smoking cessation. It is significantly more potent than nicotine at this receptor. Its affinity for this receptor is greater than for other nicotinic receptors (>500-fold for the α4 β2 nicotinic receptor and >3,500 for the α7 nicotinic receptor) and for non-nicotinic receptors and transporters (>2,000-fold). Thus, its potential for interaction with other drugs pharmacodynamically should be limited to those mediated by the α4 β2 nicotinic receptor.

Its pharmacokinetics also suggest a low risk of DDIs mediated via these mechanisms. Bioavailability is high when taken orally and is not affected by food. Plasma protein binding...
is low (<20%). Ninety-two percent of the drug is excreted unchanged, indicating that it undergoes minimal oxidative drug metabolism and hence is not susceptible to being a victim of CYP enzyme-mediated DDIs. In addition, based on in vitro studies, varenicline does not inhibit CYP enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, nor does it inhibit renal transport proteins. However, its active renal secretion is mediated by the human organic cation transporter (OCT2). Nevertheless, its therapeutic ratio is high such that a dose adjustment may not be needed when it is co-prescribed with an OCT2 inhibitor (eg, cimetidine).

Consistent with that inference, the pharmacokinetics of metformin and varenicline were not altered when they were co-prescribed in vivo. Both are substrates for OCT2. Co-administration with cimetidine (300 mg QID), an OCT2 inhibitor, increased the systemic exposure to varenicline by 29% but had no clinically significant effect. Co-administration of varenicline did not alter the pharmacokinetics of bupropion, digoxin, or warfarin.

An examination of all of the drugs (non-CNS and CNS) approved over the last decade reveals the forces that are at work in modern drug development and have implications for the future of clinical psychopharmacology. Most of these drugs are for relatively uncommon diseases but 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. 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. These newer (or biologic) drugs will be better targeted to specific disease processes. Along with the development of this new knowledge, there will likely also be a refinement of current syndromic diagnoses into new diagnoses based on pathophysiology or pathogenesis. Still, this anticipated future 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 medications to feel somewhat overwhelmed. One such explosion already occurred following the introduction of fluoxetine in 1988. While that explosion was a blessing in many ways, it nevertheless has posed serious challenges for practitioners trying to keep abreast of new developments. Today, 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 MDD, schizophrenia, Alzheimer's disease, hypertension, HIV infection, cancer, and dyslipidemia. For this reason, patients are much more likely to be on more than one medication at the same time. In fact, they are likely to accumulate preventive drug therapy as they age. These therapies can often continue for many months or years, for 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. 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 ≥8 medications doubled as a function of the number of different prescribers the patient saw. 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).

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 2). Second, patients with one psychiatric illness are at increased risk for other psychiatric disorders. Third, patients with depressive and anxiety disorders are high utilizers of healthcare services and thus may be treated symptomatically with other medications. Regardless of the reason, prescribers should be aware of this fact and take it into account when developing the treatment plan for their patients.

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 pharmacology (eg, serotonin selective reuptake inhibition). This fact 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 the rise. For example, there has been a 15-fold increase in percentage of patients on ≥3 psychiatric medications being treated at the Biological Psychiatry Branch of the National Institute of Mental Health from the early 1970s to the mid-1990s (Figure 3).
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 their combined effects added to those 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 2009, how many discrete branded drugs 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 2009 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. > 4,000
2. 8.5 X 10^15
3. 2.3 trillion
4. ~ 1 per week (i.e., 123 divided by 156 weeks or 3 years)

The above numbers are based on the number of drugs marketed according to the 2009 *Physician Desk Reference.*

**DDIs 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 prescription drugs available to prescribers. 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 software and data bases. Adverse DDIs are a significant contributor to medical injury.

To put this matter in perspective, medical injury is a serious problem estimated to cause hundreds of thousands of otherwise preventable deaths in the US each year. That estimate is larger than the deaths caused annually in the US by smoke inhalation and 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.

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 numerous otherwise safe and effective medicines from the US market over the last decade, including terfenadine, cisapride, astemizole, mibebradil, and cerivastatin. The financial impact of such withdrawals on the manufacturers of these drugs conservatively involves billions of dollars.

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.\textsuperscript{69} Finally, the US population is aging and the adverse events experienced by the elderly are markedly increased in those on ≥4 medications.\textsuperscript{70}

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 DDIs

#### 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 or 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 20–30 drugs for a practicing psychiatrist, family practitioner, or internist.

The physician should truly be an expert on these medications 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 claims 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 are 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 20–30 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 names of the medications on their personal formulary, without which it is impossible to search the medical literature on them or to recognize them 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.

While not directly a DDI issue, another significant public safety problem is medication errors. The Institute of Medicine has estimated that medication errors—wrong drug, incorrect dose, or improper use—harm at least 1.5 million people in the US every year.\textsuperscript{71} To put this matter in perspective, >3 billion prescriptions are filled in the US each year, and the number grows year over year. Medication errors can be made all along the route from prescribing to dispensing. Based on the US Pharmacopeia Medication Errors Reporting Program, up to 25% of all reported errors occur because of confusion caused by the similarity in drug names, either written or spoken. Examples include Zantac (ranitidine) for gastric acid reflux being confused with Zyrtex (cetirizine) for allergies, Flomax (tamsulosin) for benign prostate hypertrophy with Volmax (albuterol) for asthma, and Paxil (paroxetine) for depression with Plavix (clopidogrel) to decrease coagulation.

In a 2008 report, the US Pharmacopeia found 1,470 drugs implicated in medication errors, some lethal, caused by brand names or generic names that sounded or looked alike. Together, these drugs created >3,000 mixed-up pairs, nearly twice the number the organization counted in 2004.

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.

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 a psychiatric drug, they should also be aware of its mechanism(s) of action and binding profile for relevant specific receptors (Tables
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 about an individual patient’s therapeutic plan and medications. Even the highest quality of prescribing cannot work if the patient is nonadherent, 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 appropriate 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 Therapeutic Goal

Any prescription should have a clear therapeutic goal. It might be reducing a serum low-density lipoprotein, lowering 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: “Remission of depressive symptoms within 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 adherence 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 MULTIPLE MEDICATION USE

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. 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 equations are essential to understanding and avoiding DDIs:

**EQUATION 1** (©Preskorn 2007)

\[
\text{Clinical response} = \text{affinity for and intrinsic activity at a site of action (pharmacodynamics)} \times \text{drug concentration at site of action (pharmacokinetics)}
\]

\[
\text{Drug Concentration} = \frac{\text{Dosing Rate}}{\text{Clearance}}
\]

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, enzyme, or uptake pump. By binding to its target(s), the drug is capable of altering the functional status of the targets and thus altering human physiology. The ability of the drug to alter the functional status of a given regulatory protein is the mechanism underlying its potential action(s) (ie, its pharmacodynamics).

For the drug to express its potential action(s), a sufficient amount must reach the target to affect 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 sites of action the drug will bind to and to what degree. At low concentrations, the drug will bind to its highest affinity 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.

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, magnitude, and 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 (who has usual clearance) enrolled in the clinical trial to achieve a concentration sufficient to exert a sufficient mass action on the desired target 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: Absorption of the drug from the site of administration into the body, Distribution 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), Metabolism or biotransformation into more polar substances, and finally, Elimination from the body.37

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, biologic variance among patients) are summarized by the acronym GADE: Genetics, Age, Disease, and Environment. 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 nature of the effect a given dose of the drug in a specific patient may differ from its usual effect. 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.

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 10 lists five major reasons why a prescriber may use more than one drug to treat a patient.79 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 the medications the patient is taking.

The second reason listed in Table 10 is particularly relevant to psychiatry.79 Conditions such as bipolar and schizoaffective disorders are complex symptom clusters that wax and wane. Patients with these illnesses may need different medications for different phases of these illnesses. While mood stabilizers (eg, lithium) are usually the foundation for the treatment of a patient with bipolar disorder, the patient may at different phases need to have antidepressants, antipsychotics, or anxiolytics added and may even need treatment with more than one mood stabilizer. This situation is similar to that of epileptic patients. Many of these patients need to be on more than one anticonvulsant to achieve optimal control of their seizures.82

The remaining reasons listed in Table 10 are all based on planned therapeutic DDIs, whether or not the prescriber thinks in these terms.79 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 11.79

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 12 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 10.79

Beyond Psychiatric Drugs: The Total Therapeutic Regimen

The prescriber of psychiatric medications must consider 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.83 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 CYP3A and can accelerate the clearance of a number of co-prescribed medications.84,85 Smoking can induce the metabolism of drugs, such as clozapine and olanzapine, which are normally cleared by smoking-inducible CYP1A2.86 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 administered to change human physiology. 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.

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 13). The average human adult is composed of ~10–20 billion cells arranged in hierarchical 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. 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**

As mentioned previously, 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 proportionally to reach the drug concentration achieved on the usually effective dose such that the 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 concentrations fall below what is usually therapeutic, resulting in either loss of efficacy or withdrawal symptoms. Inhibition can decrease the clearance of the victim drug such that its concentrations 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.

The logic underlying pharmacokinetic interactions mediated by the induction or inhibition of CYP enzymes is outlined in Figure 4. 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 even months after one of the drugs has been discontinued.
This fact is illustrated in Figure 5 from a study examining the effect of fluoxetine on the metabolism of the CYP2D6 model substrate desipramine. In this study, genotypically normal metabolizers via CYP2D6 (>90% 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 concentrations increased >4-fold over the next 3 weeks as fluoxetine and its active metabolite, norfluoxetine, accumulated, resulting in the inhibition of CYP2D6. To this inhibition of CYP2D6 resulted in a reduction in the clearance of desipramine (Equation 2) and, hence, an increase in desipramine concentrations without a change in its dose.

On day 28, fluoxetine was discontinued but desipramine was continued at the same dose. Over the next 3 weeks, the desipramine concentrations fell as fluoxetine and norfluoxetine cleared from the body and CYP2D6 inhibition was reversed, leading to an increase in desipramine clearance. Nevertheless, desipramine concentrations 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 CYP2D6-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 individuals >65 years of age; 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.

While the study that provided the results in Figure 4 was about the effect of fluoxetine on CYP2D6, 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. For this reason, synthesis of new enzyme is required to restore usual levels of activity once the classic MAOI has been stopped. Thus, prescribers should wait >2 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 monoamine oxidase 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 DDIs**

Table 14 summarizes the major principles relevant to minimizing the risk of DDIs. Next, the major table for summarizing knowledge relevant to avoiding pharmacodynamic and pharmacokinetic DDIs are provided.

**FIGURE 4**

**HOW KNOWLEDGE OF CYP ENZYMES WILL SIMPLIFY UNDERSTANDING OF PHARMACOKINETIC INTERACTIONS**

![Image of a flowchart showing how knowledge of CYP enzymes simplifies understanding of pharmacokinetic interactions.](Image)

**FIGURE 5**

**TIME COURSE: EFFECT OF FLUOXETINE ON CYP 2D6 FUNCTION USING DESIPRAMINE AS THE PROBE DRUG**

![Graph showing the time course of desipramine plasma levels in response to fluoxetine administration.](Image)
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 SSRIs were initially approved as antidepressants, but several have subsequently gained approval labeling for the treatment of a variety of anxiety disorders. In a similar way, a number of atypical antipsychotics have gained approval for use in bipolar disorders (ie, quetiapine) and as augmentation strategies for the treatment of MDD (ie, aripiprazole). 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 7 lists the neuropsychiatric medications covered in this article by their principal mechanism of action.93 Table 16 enumerates the pharmacodynamically mediated DDIs that can occur as a result of each mechanism of action listed in Table 15. Using these tables together, the reader can determine the potential DDIs that can occur when two or more drugs listed in Table 7 are used together.72,73 Many neuropsychiatric medications including some antidepressants and atypical antipsychotics affect more than one mechanism of action under clinically relevant dosing conditions. For this reason, Tables 2 and 7–9 were developed to show the relative effect of the most commonly used neuropsychiatric medications with multiple mechanisms of action. 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 secondary target(s) divided by its binding affinity for its highest affinity target. The resulting ratio reflects the increase in concentration needed for the drug to affect its lower affinity targets in relationship to its highest affinity target. For example, quetiapine binds most avidly to the α1-adrenergic receptor and binds almost as avidly to the histamine (H1)-receptor, but requires a 23-fold increase in dose to bind to the D2 receptor (Table 2). 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 H1-receptor antagonists even though those other drugs might not have any efficacy as an antipsychotic.

The reader can use Tables 2 and 7–9 to determine how a multiple mechanism of action drug may have the potential for interacting pharmacodynamically by a mechanism other than its presumed therapeutic mechanism (as listed in Table 16) 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 can 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

Tables 1 and 17 outline potential CYP enzyme-mediated DDIs. Parenthetically, CYP-mediated DDIs are the most common, clinically meaningful type of pharmacokinetic DDIs. Table 17 lists which CYP enzymes metabolize which drugs and which drugs inhibit or induce specific CYP enzymes. Using these Tables and the logic outlined in Figure 4, the reader can predict the major potential CYP enzyme-mediated DDIs. The substrate column is limited as explained in a footnote to this table. For a more complete list, the interested reader is referred to www.drug-interactions.com.

Transport Proteins

Few molecules, including neurotransmitters and drugs, enter or leave cells or organelles unaided by energy-dependent efflux transport proteins, sometimes called “pumps.” The most well known in psychiatry are the transport proteins for the biogenic amine neurotransmitters: dopamine, norepinephrine, and serotonin. Drugs can affect the functioning of such transporter proteins. For example, SSRIs, SNRIs, and other antidepressants are thought to treat clinical depression by blocking the transport proteins (“reuptake pumps”) for one or more of the aforementioned biogenic amines. In addition to the transport proteins for these neurotransmitters, there are transport proteins that serve as chemical barriers to drugs entering the body. These include those located in the enterocytes of the gastrointestinal tract and/or hepatocytes in the liver that facilitate the exit of drugs from the body and/or facilitate their ability to distribute into specific organs (eg, those located in the blood-brain barrier and in the placenta).

By affecting the activity of these transport proteins, one drug (the perpetrator) can alter the absorption and/or distribution of another drug (the victim) in an analogous way to how a perpetrator can affect the clearance and thus the
accumulation of a victim drug by affecting the activity of the CYP enzyme which mediates the biotransformation of the victim into more polar metabolites as a necessary step in its eventual elimination from the body. DDIs mediated via effects on these transport proteins are not as well established as those mediated by CYP enzymes. Nevertheless, work in this area is growing and is important for some clinically relevant DDIs. The most well known of these interactions in psychiatry is the inhibition of lithium clearance with ibuprofen and possibly other nonsteroidal anti-inflammatory drugs. For these reasons, a brief discussion of this area is warranted in this article.

Figure 6 shows a schematic of the superfamily of energy-dependent efflux transport proteins. Of these, the best known is probably the drug transporter protein known as P-glycoprotein (PGP, aka ABCB1 or MDR1). MDR1 stands for multidrug resistance and has been used as a descriptor for this transport protein because increases in its activity have been implicated in the development of resistance by cancer cells to various cancer chemotherapeutic agents. PGP or MDR1 can produce resistance in cancer cells by either preventing chemotherapeutic agents from crossing into these cells or by facilitating their exit once they cross the cell’s membrane. Both of these actions will increase the ability of the cancer cell to survive the cancer treatment.

However, the implications for DDIs mediated by PGP go well beyond cancer as this transport protein is found in many places in the body including in enterocytes, hepatocytes, renal tubules, the blood-brain barrier, and the placenta. As with cancer chemotherapy, the function of PGP in these various locations is to either facilitate or inhibit drugs passing through these barriers between body compartments. It can thus affect the systemic bioavailability of drugs (eg, quetiapine) as well as their ability to cross into the brain or into the fetus. The gene for PGP is called MDR, and is highly polymorphic. Some of the single nucleotide polymorphisms (SNPs) in this gene are functionally important such as the variant known as C3435T. Thus, polymorphisms of these transport proteins like polymorphisms of CYP enzymes (eg, CYP2D6; Figure 1) can account for interindividual differences in sensitivity to the effects of specific drugs.

Deleting the gene for PGP or for other drug transport proteins in animals (referred to as “knock out” animals) has been one way of studying the role these transport proteins play in the absorption and distribution of various drugs. For example, the brain concentration of methadone, olanzapine, and risperidone are increased 20-fold, 3-fold, and 13-fold, respectively, in PGP knockout mice compared to normal mice.96-98 Thus, drugs that can totally inhibit the activity of this protein (ie, produce the phenocopy of a knockout animal) would be expected to produce a comparable increase in the brain concentration of these three psychiatric medications. Parenthetically, therapeutic drug monitoring would not detect this change because the plasma concentration of these three drugs in PGP knockout animals is not appreciably different from normal animals. As an aside, this scenario is an example of the occasional limitation of using plasma drug concentration as a surrogate for the brain or synaptic concentration of drugs.

Table 18 offers a partial list of drugs which are substrates for PGP.99 This Table is thus analogous to Table 17, which lists substrate drugs for various CYP enzymes. Using two different cell lines (L-MDR1 as a model for human PGP and primary porcine brain capillary endothelial cells as a model for the blood-brain barrier), Weiss and colleagues100 studied the effects on PGP of the following antidepressants: citalopram, fluoxetine, fluvoxamine, paroxetine, reboxetine, sertraline, and venlafaxine, as well as their respective major metabolites. All except for desvenlafaxine inhibited PGP activity. Paroxetine and sertraline were the most potent. Fluoxetine, fluvoxamine, and reboxetine had intermediate potency while citalopram and venlafaxine had weak potency.

**FIGURE 6**  
**SUPERFAMILY OF HEPATIC TRANSPORTERS**

SLC=sodium-lithium countertransporter; ATP=adenosine triphosphate; ABC=ATP-binding cassette; MRP=multidrug resistance-associated protein; ABCB1=P-glycoprotein; MDR1=multidrug resistant protein; P-gp=P-glycoprotein; cMOAT=canalicular multispecific organic anion transporter.

Taking this a step further, Wang and colleagues studied the potential interaction of risperidone, which is metabolized to paliperidone by CYP2D6 and is also transported across the blood-brain barrier by PGP, in mice co-administered bupropion a substantial CYP2D6 inhibitor and sertraline, a weak CYP2D6 inhibitor but more potent PGP inhibitor. They found bupropion consistent with its potent inhibition of CYP2D6 increased risperidone plasma concentrations 5.9-fold ($P<0.01$) and brain concentrations 2.2-fold ($P<0.01$) but did not change the brain-plasma risperidone concentration ratio consistent with its minimal effect on PGP. In contrast, sertraline did not change plasma risperidone concentrations consistent with its weak inhibition of CYP2D6, but increased brain concentration of risperidone and paliperidone by 1.5-fold ($P<0.05$) and 5-fold ($P<0.01$), respectively. Risperidone did not change plasma or brain concentrations of either bupropion or sertraline but did increase the plasma concentration of desmethylsertraline, the major metabolite of sertraline. These results need to be extended to humans but illustrate the potential complexity of DDIs and how affects on PGP and other drug transport proteins may be of clinical relevance.

As mentioned above, genetic polymorphisms of drug transporter proteins also occur and have been shown to be responsible for clinically important biologic variance among patients. For example, patients with drug-resistant epilepsy were more likely to have the CC rather than the TT variant of the PGP gene (OR, 2.66 with 95% CI being 1.32–5.38, $P<0.01$). Other investigators have reported that polymorphisms in this gene predict response to olanzapine in patients with schizophrenia and antidepressant treatment response in patients with clinical depression including early persistent response to paroxetine.

In summary, there is emerging evidence that drug transport proteins play a significant role in drug distribution in terms of absorption from the gastrointestinal tract, passage into the brain and placenta, and eventual excretion in the urine and bile. Moreover, there is growing evidence that altered transport activity can lead to drug resistance and to variations in organ drug concentrations. Finally, polymorphisms of PGP have been shown to influence outcomes with antipsychotics and antidepressants.

For all of these reasons, the choice of drug for a specific patient can depend upon his or her drug metabolic and transport profile. By understanding how drugs can interact pharmacokinetically either via CYP enzymes and/or drug transport proteins, the clinician can optimize clinical outcome by both increasing efficacy and reducing the risk of adverse outcomes. In fact, intentional manipulations of CYP enzyme and/or drug transport activity can improve treatment outcome in specific scenarios.

**Pharmacokinetic DDIs that are Not Metabolism Based**

This review has restricted its discussion of pharmacokinetic DDIs to those mediated by CYP enzymes and drug transporter proteins because of their clinical relevance. Nevertheless, there are other possible pharmacokinetic DDIs (Table 16) 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, 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). 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 rarely mediates a DDI of clinical significance, although it is well ensconced in the literature and the minds of physicians. The reason it is rarely clinically significant is because the resulting increased free drug persists for a clinically insignificant period before the access of the free drug to elimination mechanisms (ie, drug-metabolizing enzymes and transporters) reduces the free concentration to a new equilibrium close to the original.

The Appendix lists Web sites that the reader can use to find additional information. Web sites have the advantage of being regularly updated so that the information will stay current long after this article has been published. Software packages and their current limitations are listed in Table 19.

One major reason for software limitations 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 DDI mechanism. This situation leads to false negatives. An example is a system that reports fluoxetine’s ability to increase the level of desipramine (Figure 5) but does not warn about bupropion, which, at a dose of 300 mg/day, inhibits CYP2D6 to a degree comparable to that of fluoxetine at a dose of 20 mg/day.

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 CYP2D6 and CYP3A. That patient may not be at substantial risk for toxicity when treated with either a CYP2D6 or CYP3A inhibitor alone, but may be if treated with both inhibitors at the same time. 116 Most systems focus on pharmacodynamic or pharmacokinetic DDIs as if they were mutually exclusive when, in fact, both can occur simultaneously, often amplifying each other. 13,26

Current DDI software programs also alert but often 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 special monitoring (eg, therapeutic drug monitoring or electrocardiograms).

However, the greatest limitation is knowledge. While there are 8.5 quadrillion possible combinations of up to five drugs using the number of drugs in the 2009 Physicians’ Desk Reference, 40 there are only ~1,000 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 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 Food and Drug Administration (Table 20). 117,118

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 article 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 pharmacodynamics and pharmacokinetics of the drugs that his or her patients are taking. This article 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**

THE POTENTIAL FOR DIFFERENT, NEWER ANTIDEPRESSANTS TO BE THE PERPETRATOR OF A DDI MEDIATED BY EFFECTS ON CYP ENZYMES

<table>
<thead>
<tr>
<th>Drug</th>
<th>No or Minimal Effect (&lt;20%)*</th>
<th>Mild (20%–50%)*</th>
<th>Moderate (50%–150%)</th>
<th>Substantial (&gt;150%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>1A2, 2C9/10, 2C19, 3A3/4</td>
<td>2D6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>1A2, 2C9/10, 2C19, 2D6, 3A3/4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1A2, 2C9/10, 2C19, 3A3/4</td>
<td>–</td>
<td>2D6</td>
<td>–</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1A2, 2C9/10, 2C19, 3A3/4</td>
<td>2D6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1A2</td>
<td>3A3/4</td>
<td>2C19</td>
<td>2D6, 2C9/10</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>2D6</td>
<td>–</td>
<td>3A3/4</td>
<td>1A2, 2C19</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1A2, 2C9/10, 2C19, 2D6</td>
<td>–</td>
<td>–</td>
<td>3A3/4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1A2, 2C9/10, 2C19, 3A3/4</td>
<td>–</td>
<td>–</td>
<td>2D6</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1A2, 2C9/10, 2C19, 3A3/4</td>
<td>2D6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1A2, 2C9/10, 2C19, 3A3/4</td>
<td>2D6</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Milnacipran, mirtazapine and selegiline, based on in vitro modeling, are unlikely to produce clinically detectable inhibition of these five CYP enzymes.

*Percent increase in plasma levels of a coadministered drug dependent on this CYP enzyme for its clearance.

DDI=drug-drug interaction; CYP=cytochrome P450.

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**TABLE 2**

RELATIVE BINDING AFFINITY OF SELECTED, NEWER ANTIPSYCHOTICS FOR SPECIFIC HUMAN NEURORECEPTORS

<table>
<thead>
<tr>
<th>Drug</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;1A&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2C&lt;/sub&gt;</th>
<th>α&lt;sub&gt;1&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole&lt;sup&gt;40&lt;/sup&gt;</td>
<td>1&lt;sup&gt;†&lt;/sup&gt;</td>
<td>5</td>
<td>10</td>
<td>44</td>
<td>167</td>
<td>180</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Asenapine</td>
<td>7</td>
<td>56</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>34</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Clozapine</td>
<td>81</td>
<td>61</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1</td>
<td>692</td>
<td>23</td>
<td>1,000</td>
<td>7</td>
<td>100</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>17</td>
<td>165</td>
<td>1</td>
<td>70</td>
<td>2</td>
<td>62</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>222</td>
<td>&gt;1,000</td>
<td>17</td>
<td>11</td>
<td>488</td>
<td>1</td>
<td>400</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>2.3</td>
<td>400</td>
<td>1</td>
<td>40</td>
<td>8</td>
<td>3</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>95</td>
<td>37</td>
<td>4</td>
<td>432</td>
<td>1</td>
<td>2</td>
<td>173</td>
</tr>
<tr>
<td>Risperidone</td>
<td>25</td>
<td>&gt;1,000</td>
<td>1</td>
<td>213</td>
<td>18</td>
<td>35</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>22</td>
<td>16</td>
<td>1</td>
<td>8</td>
<td>22</td>
<td>38</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>

* Relative binding affinity = binding affinity in relationship to the drug’s highest affinity site (ie, Ki for each site divided by the Ki for drug’s highest affinity site). Hence, its relative binding affinity for its highest affinity site in the above table is 1 and for all other sites is a multiple of one as determined by this mathematical manipulation. For each drug in this table, its highest affinity and its affinity expressed in nanomolar concentration is as follows: aripiprazole, D<sub>2</sub> (0.34); asenapine, 5-HT<sub>1A</sub> (0.27); clozapine, 5-HT<sub>2A</sub> (2.59); haloperidol, D<sub>2</sub> (2.6); iloperidone, 5-HT<sub>2A</sub> (0.20); olanzapine, H<sub>1</sub> (0.087); quetiapine, α<sub>1</sub> (8.1); paliperidone, 5-HT<sub>2A</sub> (1.21); risperidone, 5-HT<sub>2A</sub> (0.15); ziprasidone, SHT<sub>2A</sub> (0.12).

† Partial agonist at the D<sub>2</sub> receptor whereas the other drugs in this table are full antagonists.

D=dopamine, 5-HT=5-hydroxytryptophan or serotonin; α<sub>1</sub>=alpha-1 adrenergic; H=histamine; M=muscarine.

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TABLE 3
MULTIPLE MEDICATION USE IN PATIENTS SEEN IN THE VETERANS AFFAIRS HEALTHCARE SYSTEM AS A FUNCTION OF AGE AND ANTIDEPRESSANT DRUG USE32-34

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Not on an Antidepressant</th>
<th>On an Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>Median number of meds.</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>% on a unique regimen</td>
<td>62</td>
</tr>
<tr>
<td>&lt;60</td>
<td>Median number of meds.</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>% on a unique regimen</td>
<td>75</td>
</tr>
</tbody>
</table>

Meds=medications; %=percentage.
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TABLE 4
PERCENTAGE (%) OF PATIENTS ON ANTIDEPRESSANTS THAT HAVE A POTENTIAL TO EXPERIENCE A DDI AS A FUNCTION OF TREATMENT SETTING38

<table>
<thead>
<tr>
<th>Treatment Setting</th>
<th>Number of patients</th>
<th>% on an antidepressant</th>
<th>% on an antidepressant plus &gt;3 other medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>2,045</td>
<td>28%</td>
<td>34%</td>
</tr>
<tr>
<td>Psychiatry clinic</td>
<td>224</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>VA Medical Centers and clinics</td>
<td>1,076</td>
<td>7%</td>
<td>68%</td>
</tr>
<tr>
<td>HIV clinic</td>
<td>66</td>
<td>1%</td>
<td>77%</td>
</tr>
</tbody>
</table>

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 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 among ethnic groups

Pharmacodynamic data

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

Clinical trial data

- An ongoing familiarity with all major clinical trials and studies

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TABLE 7
CLASSIFICATION OF NEUROPSYCHIATRIC MEDICATIONS BASED ON THEIR PRINCIPLE MECHANISMS OF ACTION12,73

<table>
<thead>
<tr>
<th>Acetylcholine</th>
<th>Selective D2 Receptor Antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase Inhibition</td>
<td>fluphenazine (eg, Prolixin)</td>
</tr>
<tr>
<td>donepezil (Aricept)</td>
<td>piperazine (Entacyl)</td>
</tr>
<tr>
<td>rivastigmine (Exelon)</td>
<td>haloperidol (eg, Haldol)</td>
</tr>
<tr>
<td>galantamine (Reminyl)</td>
<td>perphenazine (eg, Trilafon)</td>
</tr>
<tr>
<td></td>
<td>pimozide (Orap)</td>
</tr>
<tr>
<td></td>
<td>D2 Receptor Partial Agonism</td>
</tr>
<tr>
<td></td>
<td>aripiprazole (Abilify)</td>
</tr>
<tr>
<td></td>
<td>D2 Receptor Antagonism Plus Multiple Other Effects</td>
</tr>
<tr>
<td></td>
<td>See 5-HT1a, D2 and multiple other effects below.</td>
</tr>
</tbody>
</table>

Ethanol
Solubilizes electrically excitable membranes.

GABA
Barbiturates
(enhance the binding of GABA to GABA<sub>A</sub> receptors and promote rather than displace the binding of benzodiazepines)

amobarbital (Amytal) | phenobarbital (eg, Nembutal) |
butabital (eg, Butisol) | phenobarbital |
mephobarbital (Mebaral) | mepobarbital (Mysoline) |
metharbital | secobarbital (Seconal) |

Benzodiazepine Binding Site Agonism

alprazolam (eg, Xanax) | lorazepam (eg, Ativan) |
clorazepate (eg, Traxene) | midazolam (eg, Versed) |
diazepam (eg, Valium) | prazepam (Centrax) |
estazolam (eg, ProSom) | quazepam (Doral) |
flurazepam (eg, Dalmane) | temazepam (eg, Restoril) |
halazepam (Paxipam) | triazolam (eg, Halcion) |

Benzodiazepine-Like Drug
meprobamate (eg, Miltown) |

GABA Transaminase Inhibition and Stimulation of Glutaminic Acid Decarboxylase
divalproex sodium (Depakote) | valproate sodium (Depacon) |
valproic acid (Depakene) |

Promotion of Nonvesicular Release of GABA
gabapentin (Neurontin) |

Glutamate (N-methyl-D-aspartate receptor)
memantine (Namenda) |

Herbals
ginkgo biloba | St. John’s Wort |
ginseng |

Histamine (Centrally Active) (H<sub>1</sub>) Antagonism
chlorpheniramine | diphenhydramine (Benadryl) |
cyclizine (Flexeril) | hydroxyzine (Atarax) |

(Continued on next page)
### Table 7 (Cont.)
**Classification of Neuropsychiatric Medications Based on Their Principle Mechanism of Action**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Opiate Receptors</th>
<th>Serotonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha-1 Antagonism</td>
<td>alfentanil (Alfentanil)</td>
<td>buprenorphine (Buprenex)</td>
</tr>
<tr>
<td>clonidine (Catapres)</td>
<td>codeine</td>
<td>dihydroergotamine (D.H. E. 45)</td>
</tr>
<tr>
<td>Norepinephrine Uptake Pump Inhibition</td>
<td>fentanyl (eg, Sublimaze)</td>
<td>naltrexone (Nubain)</td>
</tr>
<tr>
<td>atomoxetine (Strattera)</td>
<td>hydrocodone (eg, Vicodin)</td>
<td>opium (eg, Paregoric)</td>
</tr>
<tr>
<td>cocaine</td>
<td>hydromorphone (eg, Dilaudid)</td>
<td>oxycodone (Roxicodone)</td>
</tr>
<tr>
<td>desipramine (eg, Norpramin)</td>
<td>meperidine (eg, Demerol)</td>
<td>pentazocine (eg, Talwin)</td>
</tr>
<tr>
<td>maprotiline (eg, Ludiomil)</td>
<td>methadone (eg, Dolophine)</td>
<td>propoxyphene (eg, Darvon)</td>
</tr>
<tr>
<td>Dual Norepinephrine and Serotonin (NE=SE) Uptake Pump Inhibition</td>
<td>propranolol (stab)</td>
<td>sufentanil (eg, Sufenta)</td>
</tr>
<tr>
<td>amiptylne (eg, Elavil)</td>
<td>doxepin (eg, Sinequan)</td>
<td>tramadol (Ultraform)</td>
</tr>
<tr>
<td>amoxapine (eg, Ascendin)</td>
<td>nortriptyline (eg, Pamelor)</td>
<td></td>
</tr>
<tr>
<td>clomipramine (eg, Anafril)</td>
<td>nortriptyline (eg, Lonamine)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>buspirone (eg, Buspar)</th>
</tr>
</thead>
</table>

5-HT<sub>1B/2A</sub> Agonism

<table>
<thead>
<tr>
<th>ergotamine (eg, Ergomar)</th>
</tr>
</thead>
</table>

5-HT<sub>2A</sub> and Multiple Other Receptor Antagonism—Newer Antipsychotics

<table>
<thead>
<tr>
<th>asenapine (Saphris)</th>
<th>quetiapine (Seroquel)</th>
</tr>
</thead>
</table>

5-HT<sub>2B</sub> and Multiple Other Receptor Antagonism—Older Antipsychotics

<table>
<thead>
<tr>
<th>chlorpromazine (eg, Thorazine)</th>
<th>prochlorperazine (eg, Compazine)</th>
</tr>
</thead>
</table>

Serotonin Uptake Inhibition

<table>
<thead>
<tr>
<th>dextenfluramine (Redux)</th>
<th>Fenfluramine (Pondimin)</th>
</tr>
</thead>
</table>

Selective Serotonin Uptake Inhibition

<table>
<thead>
<tr>
<th>citalopram (Celexa)</th>
<th>fluvoxamine (eg, Luvox)</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>desvenlafaxine (Pristig)</th>
<th>sibutramine (Meridia)</th>
</tr>
</thead>
</table>

5-HT<sub>2A</sub>/D<sub>2</sub> and Multiple Other Receptor Antagonism—Older Antipsychotics

<table>
<thead>
<tr>
<th>nefazodone (Serzone)</th>
<th>nortriptyline (eg, Pamelor)</th>
</tr>
</thead>
</table>

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>1B/2A</sub> Agonism”), a number of tertiary amine TCAs and related antidepressants (See the class below labeled: “Dual norepinephrine and serotonin uptake pump inhibition plus other actions”). These medications include: amitriptyline, chlorpromazine, clozapine, quetiapine, nefazodone, risperidone, thioridazine, and trazodone. See Tables 2, 8, and 9 for relative effects on neuroreceptors.

Norepinephrine

**alpha-2 Agonism**

<table>
<thead>
<tr>
<th>clonidine (eg, Catapres)</th>
</tr>
</thead>
</table>

Ion Channel Inhibition

<table>
<thead>
<tr>
<th>carbamazepine (eg, Tegretol) slows recovery of voltage-activated Na&lt;sup&gt;+&lt;/sup&gt; channels.</th>
</tr>
</thead>
</table>

dantrolene (Dantrium) interferes with the release of Ca<sup>2+</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.

mephentoin (Mesantonin) 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>1B/2A</sub> Agonism”), a number of tertiary amine TCAs and related antidepressants (See the class below labeled: “Dual norepinephrine and serotonin uptake pump inhibition plus other actions”). These medications include: amitriptyline, chlorpromazine, clozapine, quetiapine, nefazodone, risperidone, thioridazine, and trazodone. See Tables 2, 8, and 9 for relative binding affinities to this receptor by these drugs.

**Norepinephrine Uptake Pump Inhibition**

<table>
<thead>
<tr>
<th>atomoxetine (Strattera)</th>
<th>nortriptyline (eg, Pamelor)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>cocaine</th>
<th>phentermine (eg, Lonamine)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>desipramine (eg, Norpramin)</th>
<th>protriptyline (eg, Vivactil)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>maprotiline (eg, Ludiomil)</th>
<th>reboxetine (Vesper)</th>
</tr>
</thead>
</table>

5-HT<sub>1B/2A</sub>, D<sub>2</sub> and Multiple Other Receptor Antagonism—Older Antipsychotics

<table>
<thead>
<tr>
<th>chlorpromazine (eg, Thorazine)</th>
<th>prochlorperazine (eg, Compazine)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>clozapine (eg, Clozaril)</th>
<th>promethazine (eg, Phenergan)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>loxapine (eg, Loxitane)</th>
<th>promazine (eg, Sparine)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>mesoridazine (eg, Serentil)</th>
<th>thiethyperazine (Torecan)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>propiomazine (Largur)</th>
<th>thioridazine (eg, Mellaril)</th>
</tr>
</thead>
</table>

5-HT<sub>1B/2A</sub>, D<sub>2</sub> and Multiple Other Receptor Antagonism—Newer Antipsychotics

<table>
<thead>
<tr>
<th>asenapine (Saphris)</th>
<th>quetiapine (Seroquel)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>iloperidone (Fanapt)</th>
<th>risperidone (Risperdal)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>olanzapine (Zyprexa)</th>
<th>ziprasidone (Geodon)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>paliperidone (Invega)</th>
<th>paliperidone (Invega)</th>
</tr>
</thead>
</table>

5-HT<sub>1B/2A</sub>, D<sub>2</sub> and Multiple Other Receptor Antagonism

<table>
<thead>
<tr>
<th>milnacipran (Savella)</th>
<th>duloxetine (Cymbalta)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>desvenlafaxine (Pristiq)</th>
<th>sibutramine (Meridia)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>venlafaxine (Effexor)</th>
<th>venlafaxine (Effexor)</th>
</tr>
</thead>
</table>

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### Table 8

**Relative Binding Affinity of Specific Antidepressants to Specific Human Neurotransporters and Neuroreceptors**

<table>
<thead>
<tr>
<th></th>
<th>hSET</th>
<th>hNET</th>
<th>hDAT</th>
<th>p5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>h α-1</th>
<th>hM&lt;sub&gt;1&lt;/sub&gt;</th>
<th>gpH&lt;sub&gt;1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonin and norepinephrine reuptake inhibitors and antagonists at various neuroreceptors and ion channels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>4</td>
<td>34</td>
<td>&gt;1,000</td>
<td>–</td>
<td>25</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Imipramine</td>
<td>1</td>
<td>26</td>
<td>&gt;5,000</td>
<td>–</td>
<td>65</td>
<td>65</td>
<td>8</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>4</td>
<td>1</td>
<td>261</td>
<td>–</td>
<td>148</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>1</td>
<td>&gt;1,000</td>
<td>&gt;10,000</td>
<td>&gt;1,000</td>
<td>757</td>
<td>894</td>
<td>179</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1</td>
<td>&gt;1,000</td>
<td>&gt;10,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>257</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1</td>
<td>545</td>
<td>&gt;1,000</td>
<td>65</td>
<td>&gt;1,000</td>
<td>638</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1</td>
<td>620</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>560</td>
<td>&gt;5,000</td>
<td>&gt;5,000</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1</td>
<td>450</td>
<td>&gt;1,000</td>
<td>&gt;10,000</td>
<td>720</td>
<td>&gt;100,000</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>1</td>
<td>&gt;1,000</td>
<td>220</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td><strong>Selective Norepinephrine Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine†</td>
<td>21</td>
<td>1</td>
<td>&gt;1,000</td>
<td>–</td>
<td>156</td>
<td>235</td>
<td>132</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>8</td>
<td>1</td>
<td>&gt;1,000</td>
<td>875</td>
<td>&gt;1,000</td>
<td>933</td>
<td>44</td>
</tr>
<tr>
<td><strong>Dual Serotonin and Norepinephrine (SE&lt;sub&gt;E&lt;/sub&gt;-NE) Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>1</td>
<td>27</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1</td>
<td>7.5</td>
<td>504</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>1</td>
<td>9</td>
<td>&gt;1,000</td>
<td>917</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1</td>
<td>16</td>
<td>&gt;10,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td><strong>5-HT&lt;sub&gt;2A&lt;/sub&gt; Antagonist and Weak Serotonin Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>9</td>
<td>18</td>
<td>17</td>
<td>–</td>
<td>1.2</td>
<td>522</td>
<td>1</td>
</tr>
<tr>
<td>Trazodone</td>
<td>21</td>
<td>&gt;1,000</td>
<td>929</td>
<td>1</td>
<td>5</td>
<td>&gt;1,000</td>
<td>45</td>
</tr>
<tr>
<td><strong>Specific Histamine, Serotonin, and Norepinephrine Receptor Antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>&gt;100,000</td>
<td>&gt;10,000</td>
<td>&gt;100,000</td>
<td>–</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td>1</td>
</tr>
<tr>
<td><strong>Dopamine and Norepinephrine (weak) Reuptake Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>17</td>
<td>95</td>
<td>1</td>
<td>–</td>
<td>10</td>
<td>95</td>
<td>10</td>
</tr>
</tbody>
</table>

*Relative binding affinity= binding affinity in relationship to the drug’s highest affinity site (i.e., Ki for each site divided by the Ki for drug’s highest affinity site). Hence, its relative binding affinity for its highest affinity site in the above table is 1 and for all other sites is a multiple of one as determined by this mathematical manipulation. For each drug in this table, its highest affinity and its affinity expressed in nanomolar concentration is as follows: amitriptyline, H<sub>1</sub> (1); bupropion, DAT (526); citalopram, SET (1.6); desipramine NET (0.83); desvenlafaxine, SET (115); duloxetine, SET (1); fluoxetine SET (1.1); fluvoxamine SET (2.3); imipramine SET (1.41); milnacipran SET (9); mirtazapine H<sub>r</sub> (0.14); nefazodone H<sub>1</sub> (6); nortriptyline NET or H<sub>1</sub> (4.35); paroxetine SET (0.1); reboxetine NET (7); sertraline SET (0.3); trazodone 5-HT<sub>2A</sub> (7.7); venlafaxine SET (102).† This drug is also a selective norepinephrine reuptake inhibitor.

h=human; SET=serotonin transporter; NET=norepinephrine transporter; DAT=dopamine transporter; p=porcine; 5-HT=serotonin; gp=guinea pig.; H=histamine; TCAs=tricyclic antidepressants; M=muscarinic; D=dopamine; NE=norepinephrine.
TABLE 9
RELATIVE BINDING AFFINITY OF SELECTED OLDER ANTIPSYCHOTICS FOR SPECIFIC NEURORECEPTORS*

<table>
<thead>
<tr>
<th>Drug</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th>α&lt;sub&gt;1&lt;/sub&gt;</th>
<th>α&lt;sub&gt;2&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>546</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Cis-Thiothixene</td>
<td>1</td>
<td>289</td>
<td>1</td>
<td>444</td>
<td>13</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>1</td>
<td>24</td>
<td>11</td>
<td>&gt;1,000</td>
<td>26</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>Loxapine</td>
<td>12</td>
<td>1</td>
<td>20</td>
<td>&gt;1,000</td>
<td>4</td>
<td>331</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>167</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*Relative binding affinity = binding affinity in relationship to the drug’s highest affinity site (i.e., Ki for each site divided by the Ki for drug’s highest affinity site). Hence, its relative binding affinity for its highest affinity site in the above table is 1 and for all other sites is a multiple of one as determined by this mathematical manipulation. For each drug in this table, its highest affinity and its affinity expressed in nanomolar concentration is 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).

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

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TABLE 10
FIVE REASONS FOR POLYPHARMACY

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 11
PARKINSON’S DISEASE AS A MODEL OF RATIONAL COPHARMACY

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Dopa</td>
<td>Increase synthesis of central dopamine</td>
</tr>
<tr>
<td>L-Dopa + carbidopa (Sinemet)</td>
<td>Carbidopa inhibits peripheral decarboxylase to reduce the dose of L-dopa needed to increase synthesis of central dopamine (type*: pk)</td>
</tr>
<tr>
<td>L-Dopa/carbidopa + dopamine</td>
<td>Second drug potentiates the effect of released central dopamine (type*: pk)</td>
</tr>
<tr>
<td>L-Dopa/carbidopa + L-deprenyl</td>
<td>L-deprenyl increases synthesis of central dopamine and blocks its degradation (type*: pk)</td>
</tr>
<tr>
<td>L-Dopa/carbidopa + bromocriptine</td>
<td>Bromocriptine and related D&lt;sub&gt;2&lt;/sub&gt; agonists potentiate central dopamine agonism by addition of direct dopamine agonist (type*: pd)</td>
</tr>
</tbody>
</table>

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

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TABLE 12
CRITERIA FOR RATIONAL COPHARMACY IN PSYCHIATRY

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 13
THE HUMAN BRAIN

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

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

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TABLE 14
SUMMARY OF MAJOR PRINCIPLES TO AVOID ADVERSE DDIs*  

- 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 individual 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 16
MAJOR PHARMACODYNAMIC DDIs BASED ON MECHANISM OF ACTION72,73

**Acetylcholine**

**Muscarnic Acetylcholine Receptor Antagonism**
- Mitigates and can even fully reverse the EPS caused by excessive D₂ 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 acetylaminophen

**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 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 dyskinesias, hyperactivity, hyperkinesias, and psychosis induced by D agonists
- 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 5-HT syndrome when used in combination with drugs, which have agonistic effects on central NE and 5-HT systems
- Can ameliorate Parkinson’s disease
- Can cause dyskinesia, hyperactivity, hyperkinesias, 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
- Can ameliorate Parkinson’s disease
- Can cause dyskinesia, hyperactivity, hyperkinesias, and psychosis
- Can aggravate dyskinesias in conditions such as Huntington’s disease
- Above effects can be augmented by other dopamine agonists and blocked by D antagonists
- Can ameliorate Parkinson’s disease
- Can cause dyskinesia, hyperactivity, hyperkinesias, and psychosis
- Can aggravate dyskinesias in conditions such as Huntington’s disease
- Above effects can be augmented by other dopamine agonists and blocked by D antagonists
- Can ameliorate Parkinson’s disease
- Can cause dyskinesia, hyperactivity, hyperkinesias, and psychosis
- Can aggravate dyskinesias in conditions such as Huntington’s disease
- Above effects can be augmented by other dopamine agonists and blocked by D antagonists
- Can ameliorate Parkinson’s disease
- Can cause dyskinesia, hyperactivity, hyperkinesias, and psychosis
- Can aggravate dyskinesias in conditions such as Huntington’s disease
- 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

(continued on next page)
MAJOR PHARMACODYNAMIC DDIs BASED ON MECHANISM OF ACTION

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 Alzheimer's Disease
- 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, barbiturate-like drugs
- Benzodiazapine binding site agonism
- Promotion of nonvesicular release of GABA

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)
- Benzodiazapine binding site agonism (See barbiturates above)
- Benzodiazapine-like drugs (See barbiturates above)
- GABA transaminase inhibition and stimulation of glutaminic 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 C<sub>2</sub>-agonists, angiotension converting enzyme inhibitors, β-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 C<sub>2</sub>-agonist can cause clinically serious hypertensive rebound.
- Mirtazapine is an alpha-2 adrenergic antagonist.
- By decreasing norepinephrine outflow, C<sub>2</sub>-adrenergic agonists would be expected to antagonize the effects of neuropsychiatric medications that block norepinephrine uptake pumps and MAOIs.

alpha-2 Antagonism
Effects and interactions are the converse of C<sub>2</sub>-agonism

Norepinephrine Uptake Pump Inhibition
These drugs have 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 C<sub>2</sub>-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 serotonin 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.

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

**5-HT1B/D 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-HT2 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-HT2A and D2 Receptor Antagonism**

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

**5-HT2A, D2, 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**

**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-HT1A partial agonists and 5-HT1B/D 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 (NE>SE) Uptake Pump Inhibition**

See comment under dual norepinephrine and serotonin uptake pump inhibition

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**TABLE 16 (CONT.)**

**MAJOR PHARMACODYNAMIC DDIs BASED ON MECHANISM OF ACTION**

| EPS=extrapyramidal side effects; D=dopamine; NE=norepinephrine; 5-HT=serotonin; COMTIs=catechol-O-methyltransferase inhibitors; MAOIs=monoamine oxidase inhibitors; CNS=central nervous system; GABA=γ-aminobutyric acid; H=histamine; SE=serotonin. |

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### TABLE 17

**DRUGS CATEGORIZED AS SPECIFIC CYP ENZYME SUBSTRATES, INHIBITORS, OR INDUCERS TO PERMIT PREDICTION OF CYP-MEDIATED DRUG-DRUG INTERACTIONS**

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TABLE 17 (CONT.)
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<td>2C19</td>
<td>methylcholanthrene</td>
<td>rifampin</td>
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<td>2D6</td>
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<td>rifampin</td>
<td>rifampin</td>
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<td>2E1</td>
<td>nafcillin</td>
<td>rifampin</td>
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<td>3A4,5,7</td>
<td>beta-naphthoflavone</td>
<td>rifampin</td>
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<td>rifampin</td>
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<td></td>
<td>tobacco</td>
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</table>

The above list is restricted to select CNS-active drugs prescribed in the US, except for the drugs listed under the heading “other.” These drugs are shown because they are of special relevance to this article. Drugs in bold have a psychiatric indication per the FDA. For a complete list go to: http://medicine.iupui.edu/clinpharm/ddis/. CYP=cytochrome P450; →=primary metabolic route for the substrate indicated via the cytochrome P450 indicated; NAPQI=N-acetyl p-benzoquinone imine; Nor=the metabolite of the drug indicated; HIV=human immunodeficiency virus; CNS=central nervous system; US=United States; FDA=Food and Drug Administration.


TABLE 18
P-GP SUBSTRATES (PARTIAL LIST)99

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Antipsychotics</th>
<th>Antihistamines</th>
<th>HIV protease inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• amitriptyline</td>
<td>• olanzapine</td>
<td>• fexofenadine</td>
<td>• indinavir</td>
</tr>
<tr>
<td>• nortriptyline</td>
<td>• risperdone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• citalopram</td>
<td>• paliperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• paroxetine</td>
<td>• quetiapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• venlafaxine</td>
<td>• aripiprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>•</td>
<td>• clozapine</td>
<td>• lopinavir</td>
<td></td>
</tr>
<tr>
<td>•</td>
<td>• ziprasidone</td>
<td></td>
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</tr>
</tbody>
</table>

Antipsychotics

Atypical Antipsychotics

| • olanzapine | • risperidone | • paliperidone | • quetiapine | • aripiprazole | • clozapine (?) | • ziprasidone (?) |
|• clozapine |• risperidone |• paliperidone |• quetiapine |• aripiprazole |• clozapine (?) |• ziprasidone (?) |

Antihistamines

| • fexofenadine | • loperamide | | | |

HIV protease inhibitors

| • indinavir | | | |


TABLE 19
CURRENT DDI SOFTWARE PACKAGES AND THEIR LIMITATIONS112-115

<table>
<thead>
<tr>
<th>Drug Facts and Comparisons</th>
<th>Epocrates</th>
<th>Hansten’s</th>
<th>Mhc.com/Cytochromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromedex</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• 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 20
REPORTING ADVERSE DRUG REACTIONS117,118

<table>
<thead>
<tr>
<th>MedWatch: 1-800-FDA-1088</th>
<th>Fax: 1-800-FDA-0178</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report online at: <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a></td>
<td>Practitioner reporting online at: <a href="http://www.usp.org">www.usp.org</a></td>
</tr>
</tbody>
</table>

APPENDIX

WEB SITES26,36,107-111
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.

Description

Psychiatric Drug Interaction

Cytochrome P450 Interactions

Herbal Interactions

HIV Drug Interactions

HIV Drug Interactions

Grapefruit Juice – Drug Interactions

FDA Food and Drug Interactions

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


REFERENCES

1. Voltaire. 1694-1788.


