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2004 Guide to Psychiatric Drug Interactions

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Focus Points

- In a drug-drug interaction (DDI), the presence of a second drug alters the nature, magnitude, or duration of the effect of a given dose of a first drug. These interactions can be therapeutic or adverse, planned or unintended, but are always determined by the pharmacodynamics and pharmacokinetics of the drugs involved rather than their therapeutic indication.
- 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.
- To avoid adverse DDIs, the prescriber must keep in mind fundamental principles of pharmacology and good clinical management.
- The prescriber must know all of the medications that the patient is taking and be able to use available knowledge about their pharmacodynamic and pharmacokinetic mechanisms to minimize the risk of untoward DDIs.

Abstract

Why should physicians be concerned about drug-drug interactions (DDIs)? DDIs have the potential for causing untoward outcomes, including morbidity and even mortality for the patient, liability for the prescriber, and increased costs for the healthcare system. The risk of unintended and untoward DDIs is increasing in concert with both the increasing number of pharmaceuticals available and the number of patients on multiple medications. A recent survey found that 10% of all Americans >18 years of age were taking five or more prescription medications. Additional studies have found that patients on psychiatric medications, such as antidepressants, are on more medications than patients not on psychiatric medication. In addition, medications interact not on the basis of their therapeutic use but on the basis of their pharmacodynamics and pharmacokinetics. For these reasons, the prescriber of psychiatric medications must consider all of the medications the patient is taking. This educational review discusses major pharmacologic principles to guide the safe and effective use of multiple medications with a focus on neuropsychiatric medications. It also presents tables outlining major pharmacodynamic and pharmacokinetic mechanisms mediating DDIs relevant to the patient on psychiatric medications.

Introduction

A drug-drug interaction (DDI) occurs when the presence of a coprescribed drug (the perpetrator) alters the nature, magnitude, or duration of the effect of a given dose of another drug (the victim). "Altered nature" means that the effect produced when the two drugs are used together is qualitatively different than would be expected when either drug is used alone. An example is serotonin syndrome, which consists of marked autonomic instability and can be fatal. This syndrome can occur when a serotonin uptake pump inhibitor is used in combination with a monoamine oxidase inhibitor (MAOI).[1] "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 either is shorter or longer lived than would normally be expected for the dose given.

The goal of this guide is to provide a quick reference for prescribers about some of the major psychiatric DDIs. Furthermore, it presents general concepts which can aid prescribers in avoiding untoward DDIs when possible and quickly recognizing them when they occur. This way, corrective steps can be instituted to minimize the consequences. This guide is not intended to be comprehensive or authoritative. Given the speed with which new drugs are entering the market and new discoveries about the mechanisms underlying DDIs are being made, the authors recognize that this educational 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 (Appendices I and II). This general guide provides an introduction to the topic and serves as a gateway to ready sources of additional information via the Internet.

Both authors maintain Web sites relevant to DDIs. Dr. Flockhart's Web site[2] summarizes data on cytochrome P450 (CYP) enzymes and the drugs they metabolize and outlines which drugs inhibit or induce CYP enzymes. This information can be used to predict and avoid DDIs mediated by this mechanism. Dr. Preskorn's Web site[3] provides content on topics relevant to the

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safe and effective use of psychiatric medications. For example, under "Columns, Section 1: Polypharmacology," Dr. Preskorn presents and discusses real life case examples of how DDIs present clinically and the mechanisms responsible for the DDI.[4] The authors will refer to these and other Web sites as a reference for the reader who wants a more extended discussion of a topic or for those who want to check for updates after this guide has been published.

This guide has several other limitations, starting with the one imposed by its title: drugs do not interact on the basis of their therapeutic area (eg, psychiatric 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).[5] For this reason, the authors acknowledge the limitations inherent in focusing on therapeutic class—even one as broad as psychiatric or neuropsychiatric medications. In fact, the authors will reclassify the drugs principally covered in this guide into other 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 mechanisms relevant to clinically significant DDIs.

While the focus of this review is principally on neuropsychiatric medications, the authors will also address the effects of psychiatric on nonpsychiatric medications and vice versa where appropriate when covering DDIs. These are most important for the prescriber who treats patients with conditions broadly defined as psychiatric illnesses. With these caveats, this guide will focus on neuropsychiatric medications.

This guide will first review the scope of the problem, discuss strategies and approaches to avoiding untoward and unintended DDIs, and then present summary figures and tables highlighting major DDIs involving psychiatric medications.

Polypharmacy: The Real Landscape of Clinical Prescribing

Over the last 15 years, prescribers of psychiatric medications have been blessed with an ever-expanding array of options to treat a wide variety of psychiatric maladies. The explosion in psychiatric medications began with the introduction of fluoxetine (Prozac) in 1988[6] and is likely to continue and even accelerate in the future as a result of the human genome project and the characterization of novel therapeutic targets in the human brain.

While a blessing in many ways, this development poses serious challenges for practitioners trying to keep abreast of new developments. The prescriber has more therapeutic options, each with different pharmacodynamics and pharmacokinetics, to understand and weigh.

Over the last several decades, treatment has moved from a focus on time-limited therapy (ie, a few weeks) of an acute illness (eg, antibiotics for an acute infection) to preventive or maintenance therapy for chronic illnesses as diverse as major depressive disorder (MDD), schizophrenia, Alzheimer's disease, hypertension, human immunodeficiency virus infection, and atherosclerosis. As a result of this change in focus, patients are more likely to be on more than one medication at the same time.[7-10] In fact, they are likely to accumulate preventive therapy as they age, which can often continue for many months or years, to perhaps the entire remaining lifespan of the individual once started. As a result, the potential for DDIs increases over the lifespan of the individual.

In addition to the above general principle, patients with psychiatric illnesses such as MDD are frequently on multiple other medications for a variety of reasons, regardless of whether they are being seen by a psychiatrist or another type of healthcare provider (Table 1).[3,11]

There are undoubtedly numerous reasons for this phenomenon. First, psychiatric illnesses such as MDD have an increased frequency in patients with other medical illnesses (Figure 1).[12-16] Second, patients with one psychiatric illness are at increased risk for other psychiatric disorders.[17] Third, patients with depressive and anxiety disorders are high utilizers of healthcare services and thus may be treated symptomatically with other medications.[15,18-23]

These factors likely help explain why in 1989 patients seeing a psychiatrist were six times more likely to be on multiple psychiatric medications, compared with patients seeing a primary care physician.[24] The use of multiple psychiatric medications has also increased in favor over the last 2 decades, reflecting both the increased availability of effective medications and the fact that they have a more focused pharmacology. The latter leads to better tolerability but may also limit efficacy and thus require the use of more medications to optimize patient outcomes. The use of multiple psychiatric medications to treat patients is on the rise; there was a 15-fold increase in percentage of patients on three or more psychiatric medications being seen at the Biological Psychiatry Branch of the National Institute of Mental Health from the early 1970s to the mid 1990s (Figure 2).[25]

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

To underscore the complexity of such DDIs, consider the following questions, which help to illustrate the size of the problem: (1) In 2003, how many discrete chemical entities could a physician prescribe for his/her patient? (2) Given the number of drugs, how many different combinations (up to five drugs) could the physician prescribe for his/her patient? (3) The first new drug approved in 2003 could be prescribed in how many different combinations (up to five 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 United States market every year over the last 3 years?

The answers are: (1) >3,200 different drugs; (2) 2.8×10^{15}; (3) 4.4 trillion; and (4) approximately 18, or one every 3 weeks.

To further put the numbers in perspective, consider that 10% of all Americans >18 years of age were taking five or more prescription drugs in the last week. These numbers provide a frame of reference which explains why understanding and minimizing the risk of untoward and unintended DDIs is important and daunting.

Drug Interactions and Medication Errors

Given the above numbers, DDIs are, not surprisingly, a serious cause of con-

cern for the US healthcare system. They are so numerous that the dictum to "do no harm" is seriously challenged. As illustrated by the answers to the questions above, this situation is in part due to the large number of new prescription drugs available to prescribers. For medical students who graduated from medical school in 2001, 115 new prescription drugs had been approved by the Food and Drug Administration during the time they were in medical school.[26] In contrast, students graduating in 1973 had to contend with only 57 new drugs being approved during their four years of medical school.[26] The number of drugs available over the counter has also increased.

An ignorance of important interactions threatens trust in physicians and other prescribers. As the number of prescribed medications has increased over the past 20 years, so have the number of possible interactions between therapies. These interactions have increased to the point where prescribers universally find it impossible to remember all conceivable interactions and are forced to rely on electronic media. From 7,000 to as many as 98,000 deaths are caused by adverse drug events each year, more than those caused by smoke inhalation or airplane accidents, causes of death for which the US has generated elaborate, nationwide safety control systems.[27]

In 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 understated. DDIs are not the entire cause of adverse drug events, but they are a significant contributor, as indicated by the number of medicines withdrawn from the market due to drug interactions in the last 6 years, and by a growing number of significant interactions that result from co-medication with herbal nutritional supplements, a market on which the US spends more than they do on prescription medicines.[28]

Lastly, the population is aging. It has been clear for many years that adverse events experienced by the elderly are markedly increased in those who take more than four medications at once.[29]

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.

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 2).

DDIs are of paramount importance to health professionals who practice in the pharmaceutical industry. This is because the number of prescription medicines that were initially approved by the FDA as safe and effective but which then had to be removed from the market due to unacceptable DDIs, including terfenadine, cisapride, astemizole, mibefradil, and, most recently, cerivastatin, is considerable.[30] The financial impact of such withdrawals on companies conservatively involves billions of dollars, but the harm to patients may also be substantial, especially if, as in the case of the antihistamines, the drug is taken with a relatively minor health complaint and patients do not expect that they are assuming a risk of sudden cardiac death by treating their allergies.[31]

Strategies to Minimize Adverse Outcomes From Unintended DDIs

A Personal Formulary: Concept and Criteria

The value of a personal formulary in an era of polypharmacy and pervasive and potent marketing cannot be overemphasized. Although all physicians are taught pharmacology in medical school, it is clear to anyone who has been out of medical school for >5 years that many, if not most, of the drugs that are commonly prescribed today were not available during their training. A personal formulary is the central tool of any prescriber's armamentarium. Such a formulary should consist of the drugs that are used virtually every day in the clinician's practice; rational prescribing in an era when so many drugs are available is close to impossible without it.

A personal formulary basically consists of a list of drugs that a particular physician is intimately familiar with. Inevitably, this list cannot be a large number of drugs. For the drugs in their personal formulary, the physician should be familiar with generic and brand names, pharmacokinetics, pharmacodynamics, adverse effects, and potential DDIs. The physician should truly be an expert on a small number of medications that he or she uses commonly. A high level of knowledge about a few drugs insulates the physician against trivial advertising and protects one's patients from prescribing errors. The number of drugs in a personal formulary will vary, but it is generally reasonable for a practicing psychiatrist, family practitioner, or internist to have 10–15 such drugs as the core of his or her personal formulary. The essential elements of knowledge that the physicians should know about each drug in their personal formulary is listed in Table 3.

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. If nothing else, these criteria allow the prescriber a means of focusing his or her attention within the sea of the medical literature. Thus, physicians become real experts in the use of a small number of drugs important to their practice. In the 21st century, it is not enough to be an excellent diagnostician familiar with the use of laboratory and procedural testing: being expert in treatment is also required, and that requires an intimate knowledge not of all drugs available, but of 10–15 that are commonly used. This foundation of knowledge can then serve as a basis for the evaluation of new drugs as they appear.

Generic Names

At a minimum, a prescriber should be aware of the generic name of a medication on their personal formulary, without which it is impossible to search the medical literature on it or to recognize it on a board exam. As medicine becomes more international and the world becomes smaller, the physician must be aware that medications have different brand names in different countries, and the brand name used in the US may not be the same as that used elsewhere (Table 4).[32] The use of the generic name in prescriptions allows cheaper generic drugs to be used when they are available. Despite claims

to the contrary, there are only a small number of examples where an approved generic is not an effective substitute for the brand name drug.

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

A list of generic names of psychiatric drugs used in the US and their brand names is included in Table 5.[33] 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.

Adverse Effects

While a large number of possible adverse effects of any drug may be listed in the label that is available in the *Physicians' Desk Reference*,[34] relatively few matter to an individual patient. The prescribing physician is in a unique position to assess which adverse effects are relevant to which patient through careful consideration of both the patient and the medication in question. No one else is in this position and many patient surveys over the years clearly show that patients much prefer that their physician acquaint them with the benefits and side effects of drugs that the physician prescribes.[35] That is not to say that pharmacists and nurses are not also important to the prescribing process, but instead that physicians have a central role in the prescribing process that they must recognize. Patients expect physicians to educate them about their medications, and greatly appreciate when a physician takes time to explain the side effects of a medicine they have prescribed.

Pharmacokinetics

Prescribers should be aware of the routinely used doses and the serum half-life of the drugs they frequently use. In the case of psychiatric drugs, they should also be aware of the mechanism of action, and of the potency of interaction with specific receptors (Tables 5–8). This basic information can guide prescribing in a number of valuable ways, particularly by making prescribers aware of the potential DDIs and consequences.

The Therapeutic Alliance

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

Establishment of a Therapeutic Goal

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

Conceptual Framework for Prescribing in an Era of Polypharmacy

Principles of Pharmacology

A DDI occurs when the presence of a coprescribed 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 clearly be therapeutic or adverse, intended or unintended, but they are always determined by the pharmacodynamics and pharmacokinetics of the coprescribed drugs. When one drug is used to treat an adverse effect or to boost the therapeutic benefit of another drug, the prescriber wittingly or unwittingly is may cause therapeutic DDI.[36]

The focus of this guide, however, is to minimize the risk of an unintended and untoward DDI and therefore will not consider therapeutic DDIs.

Given the above, the following two equations are essential to understanding and avoiding DDIs:

Equation 1

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

Equation 2

$$\text{drug concentration} = \frac{\text{dosing rate}}{\text{clearance}}$$

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

able in Equation 1. Drug concentration in relation to the drug's binding-affinity profile determines what site of action the drug will bind to and to what degree. At low concentrations, the drug will bind to its most potent target. As the concentration increases, the drug will bind more substantially to that target until it is saturated. It may also begin binding to lower affinity targets when its concentration reaches a sufficiently high degree relative to its binding affinity for a second target(s).[37,38]

Equation 2 illustrates that a drug concentration is a function of the dosing rate the patient is taking relative to their ability to clear the drug. This equation explains why clearance is as important as dose in determining the nature, the magnitude, and the duration of a drug's effect on the patient. Clinical trials are population pharmacokinetic studies in which the goal is to determine the usual dose needed for the usual patient (ie, usual clearance) enrolled in the clinical trial to achieve a concentration sufficient to engage the desired target sufficiently to produce the best balance between efficacy and safety/tolerability. Thus, the second variable in Equation 1 is the drug's pharmacokinetics (or drug movement), which has four phases summarized by the acronym "ADME": 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.[5]

The last variable in Equation 1 is the interindividual differences among patients, which can shift the dose response curve making patients either more or less sensitive to the effect of the drug. These differences (ie, biological variance among patients) are summarized by the acronym "GADE": 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 the nature of the effect of the drug in a specific patient may differ from the usual effect produced by a given dose of the drug. Thus, DDIs occur when one drug (the perpetrator) changes the effect of a given dose of another drug (the victim) by either interacting with it pharmacodynamically or pharmacokinetically (ie, the first and second variables in Equation 1). This concept is the essential principle underlying DDIs and the basis for the rest of this guide.[3]

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 9 lists five major reasons why a prescriber may use more than one drug to treat a patient.[3,36] The first reason is the most obvious: the patient has more than one disease process and the prescriber must employ one or more agents for each disease. In this example, the prescriber is not planning a DDI, though one may occur because drugs interact on the basis of the mechanisms underlying their pharmacodynamics and pharmacokinetics, rather than on the basis of their therapeutic indication. For this reason, the prescriber of psychiatric medications must be aware of and consider all of the medications the patient is taking.

The second reason listed in Table 9 is particularly relevant to psychiatry.[3,36] Conditions such as bipolar and schizoaffective disorder have complex symptom clusters which wax and wane over the course of the illness. Patients with these illnesses may need different medications for different phases of their illness. While mood stabilizers (eg, lithium) are usually the foundation for the treatment of a patient with bipolar disorder, at different phases of the illness the patient may need to have antidepressants, antipsychotics, or anxiolytics added and may even need treatment with more than one mood stabilizer. This is similar to patients with epilepsy, many of whom need to be on more than one anticonvulsant to achieve optimal control of their seizures.[39,40]

The remaining reasons listed in Table 9 are all based on planned therapeutic DDIs, whether the prescriber thinks in these terms or not.[3,36] When a second drug diminishes, amplifies, or speeds the onset of a first drug, that effect 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 10.[3,36] 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 11 lists a series of features that can be used to rationally prescribe treatment with two or more psychiatric medications together to accomplish the last three goals listed in Table 9.[3,4,36]

Beyond Psychiatric Drugs to the Total Therapeutic Regimen

The prescriber of psychiatric medications cannot simply focus on those medications but must examine all of the medications the patient is taking, including over-the-counter (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 reabsorption.[41] The duration of the effect of illicit substances can be prolonged by coprescribed drugs, which inhibit the enzymes responsible for clearing the illicit substance. St. John's wort is a substantial inducer of CYP 3A and thus can accelerate the clearance of a number of co-prescribed medications.[42] Smoking can induce the metabolism of drugs such as clozapine, which are normally cleared by smoking-inducible CYP 1A2.[43] 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 DDI 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 rea-

son, such "masked" DDIs can ironically lead to the use of more medications to treat the apparent worsening of the primary condition or to treat the apparent emergence of a new condition.

All drugs, except anti-infectives, are given to change human physiology.[44] 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.[42]

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 12).[45] The average adult human is composed of approximately 10–20 billion cells arranged in a hierarchal and integrated system. 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.[3] Their detection is dependent on the careful assessment at the time of a medcheck by the prescriber as discussed in the next paragraph.

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. Thus, the result of psychiatric DDIs could 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 guide and of all information systems in clinical psychopharmacology. There is much more that needs to be known. In the interim, the goal of this guide is to summarize what is known, to explain the limits of current knowledge, and to define good clinical practices as they relate to avoiding untoward DDIs.

Proper Use of Therapeutic Drug Monitoring

Equation 1 illustrates that drug concentration determines what site(s) of action are engaged and to what degree, while Equation 2 illustrates that drug concentration is the dosing rate divided by the clearance. By re-arranging 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 than usual, then the dosing rate must be increased proportionately to reach the usual drug concentration achieved on the usually effective dose; in other words, the usual site(s) of action must be engaged to the usual degree associated with optimal response as determined by the registration trials that lead to the marketing of the drug. Thus, the goal of therapeutic drug monitoring (TDM) is not to simply know whether the concentration is therapeutic but to know whether the patient's ability to clear the drug is usual or not. If not, the results of TDM can provide a rational basis for determining what sort of an adjustment in the dosing rate must be made to compensate for the patient's unusual clearance.

This issue is of critical importance when understanding and avoiding untoward effects mediated by the co-prescription of a drug capable of either inducing or inhibiting the enzymes responsible for the clearance of the victim drug. Induction can increase the clearance of the victim drug such that its levels fall below what is usually therapeutic, resulting in either loss of efficacy or withdrawal symptoms.[46] Inhibition can decrease the clearance of the victim drug such that its levels rise causing consequences, which may range from an increase in the frequency and severity of dose-dependent adverse effects, such as extrapyramidal side effects 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 3.[3,32] This logic forms the basis for the section on CYP enzyme-mediated DDIs with psychiatric medications.

Time Course of Interactions

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

This fact is illustrated in Figure 4 from a study examining the effect of fluoxetine on the metabolism of the CYP 2D6 model substrate desipramine.[47] In this study, genotypically normal metabolizers via CYP 2D6 (>95% of the population) were first treated with desipramine 50 mg/day for 7 days to achieve steady-state conditions. On day 8, fluoxetine 20 mg was added to their regimen. Without changing the dose of desipramine, its levels increased >4-fold over the next 3 weeks as fluoxetine and its active metabolite, norfluoxetine, accumulated, resulting in the inhibition of CYP 2D6. The inhibition of CYP 2D6 resulted in a reduction in the clearance of desipramine (Equation 2), hence an increase in desipramine levels without a change in dose.

On day 28, fluoxetine was discontinued but desipramine was continued at the same dose. Over the next 3 weeks, the desipramine levels fell as fluoxetine and norfluoxetine cleared from the body and CYP 2D6 inhibition in parallel was reversed, leading to an increase in desipramine clearance. Nevertheless, desipramine levels even 3 weeks after fluoxetine was discontinued were still double what they were before fluoxetine was added because norfluoxetine was still present in the body and still inhibiting CYP 2D6-mediated clearance. This time course is consistent with the fact that the half-lives of fluoxetine and norfluoxetine in young healthy individuals (such as those in this study) are 2–4 days and 7–15 days, respectively. Of note, the

average half-life of norfluoxetine in healthy individuals ≥65 years of age is 3 weeks; thus it takes an average of 4 months to reach steady-state once the drug is started in older individuals, and 4 months to completely clear once the drug is discontinued.[48]

While the study that provided the results in Figure 4 was about the effect of fluoxetine on CYP 2D6,[47] it graphically illustrates the point that the effect of a coprescribed perpetrator drug (eg, fluoxetine) on the response to the victim drug (eg, desipramine) can continue to increase for weeks after the perpetrator has been started and can persist for weeks after the perpetrator has been stopped. Sometimes that is because the perpetrator has a long residual time in the body, as in the case of fluoxetine, and sometimes it is because the perpetrator's effect persists long after it has been cleared. An example of the latter would be the classic MAOIs, which cause irreversible inhibition of that enzyme; synthesis of new enzyme is required to restore usual levels of activity once that classic MAOI has been stopped.[48,49] 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 protein 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.[50] These delayed onsets and offsets are not simply limited to pharmacokinetic interactions as witnessed by MAO inhibition (which is a pharmacodynamic interaction) but can be applied to all interactions in which the effect of the perpetrator persists for a sustained period after the perpetrator has been discontinued (eg, receptor supersensitivity or subsensitivity).

How to Avoid DDIs

Table 13 summarizes the major principles relevant for minimizing the risk of DDIs. Next, the major tables for summarizing knowledge relevant to avoiding pharmacodynamic and pharmacokinetic DDIs are provided.

Pharmacodynamic DDIs

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

Table 5 lists the neuropsychiatric medications to be covered in this guide by their principal mechanism of action. Table 14[51] enumerates the pharmacodynamically mediated DDIs that can occur for each mechanism of action listed in Table 5. Using these tables together, the reader can determine the potential DDIs that can occur when any drug in Table 5 is used with a drug having a mechanism that interacts with its mechanism of action (Table 11).[32,51]

A number of neuropsychiatric medications including tertiary amine tricyclic antidepressants and atypical antipsychotics affect more than one mechanism of action under clinically relevant dosing conditions. For this reason, Tables 6–8 have been developed to show the relative effect of the most commonly used neuropsychiatric medication with multiple mechanisms of action.[34,52-56] In these tables, the most potent binding site of the drug was assigned the value of 1 and its relative binding affinity for other targets was expressed as its binding affinity for that target divided by its binding affinity for its most potent target. The resulting ratio reflects the increase in concentration needed for the drug to affect its less potent target in relationship to its most potent target. For example, quetiapine binds most avidly to the α_1 adrenergic receptor and binds almost as avidly to the H_1 receptor, but requires a 23-fold increase in dose to bind to the dopamine D_2 receptor (Table 6). 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 histamine H_1 receptor antagonists even though those other drugs might not have any efficacy as an antipsychotic medication.

The reader can use Tables 6–8 to determine how a multiple mechanism of action drug may carry the potential for interacting pharmacodynamically by a mechanism other than its major presumed therapeutic mechanism (as listed in Table 5) 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 which is likely being achieved in the patient. The reader can also use this information to determine whether he or she might wish to employ TDM to further establish the actual concentrations being achieved in their specific patient and relate that to both relative binding affinity for its multiple targets as well as relative to the concentration usually achieved on the dose being used. The clinician could use TDM to determine whether his or her specific patient has unusually fast or slow clearance relative to the usual clearance found in the registration trials and whether the patient is developing concentrations comparable to or concentrations much higher or lower than those found in registration trials.

Pharmacokinetic Tables

These tables outline potential CYP enzyme-mediated DDIs. Parenthetically, CYP-mediated DDIs are the most common, clinically meaningful type of pharmacokinetic DDIs. Table 15 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 3, the reader can predict the major potential CYP enzyme-mediated DDIs.[3,32]

Pharmacokinetic Drug Interactions That Are Not Metabolism-Based

This guide restricted its discussion of pharmacokinetic DDIs to those mediated by CYP enzymes because of their clinical relevance. Nevertheless, there are other possible pharmacoki-

netic DDIs (Table 16)[57] worth briefly mentioning as follows: the chelation of drugs in the gastrointestinal tract by iron salts prescribed to treat anemia or by antacids with high aluminum content; interactions that occur prior to the administration of intravenous (IV) drugs due to the incompatibility of IV solutions; interaction with secreting drug transporters that line the renal tubules and the blood-brain barrier (eg, lithium intoxication due to coadministration with ibuprofen and possibly other nonsteroidal anti-inflammatory drugs); and nutritional interactions that deplete the co-factors required for the phase II metabolism of some drugs (ie, reduced acetylation and glycosylation due to persistent hypoglycemia or clinically significant malnutrition).[58]

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 α-acid glycoprotein. This mechanism virtually never mediates a DDI of clinical significance, although it is well ensconced in the literature and the minds of physicians. This mechanism is virtually never clinically significant because the resulting increased free drug persists for a very short and clinically insignificant period before the access of the same free drug to elimination mechanisms, such as enzymes transporters, reduces the free concentration to a new equilibrium very close to the original.[59]

Appendices

Appendix I lists Web sites that the reader can use to find additional information.[2,3,60-64] Web sites have the advantage of being regularly updated so that the information will stay current even after this guide has been published. Appendix II lists software packages[65-69] and the current limitations of such software.

One major limitation is that there are no standard guidelines for producing such drug alert systems in terms of what constitutes sufficient evidence to list an interaction as possible. Thus, software packages can either be overly conservative and can list interactions based on theory rather than fact or based on a single case report of dubious validity. This, in turn, can cause a high rate of situation, false positive alerts which can again lead the prescriber to ignore the system (ie, "the boy who cried wolf").

Other systems may require that a formal study be conducted showing that the interaction occurs; they do not generalize the interaction to other drugs with the same mechanism. This situation leads to false negatives. An example of the latter would be a system that reports that fluoxetine elevates the level of desipramine on the basis of the study illustrated in Figure 4 but does not warn about bupropion, which, at a dose of 300 mg/day, inhibits CYP 2D6 to a degree comparable to that of fluoxetine 20 mg/day.[34]

Most drug alert systems only consider the effect of drug A on drug B, whereas many patients are on multiple drugs that may interact in complex ways. An example would be a patient who is taking a drug equally cleared by CYP 2D6 and CYP 3A. That patient may not be at substantial risk for toxicity when treated with either a CYP 2D6 or CYP 3A inhibitor alone but may be if treated with both inhibitors at the same time.[4] Most systems focus on pharmacodynamic or pharmacokinetic DDIs as if they were mutually exclusive, when in fact both can occur simultaneously and hence amplify each other.[4,70]

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

However, the greatest limitation is knowledge. While there are 2,800 trillion possible combinations of up to five drugs using the number of drugs in the 2003 *Physicians' Desk Reference,*[34] there are <700 formal DDI studies published, 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 thus led to generalizable knowledge. For this reason, the authors encourage the readers to write up their cases and publish them in the medical literature, as well as to use the adverse drug reaction reporting system developed by the FDA (Table 18).

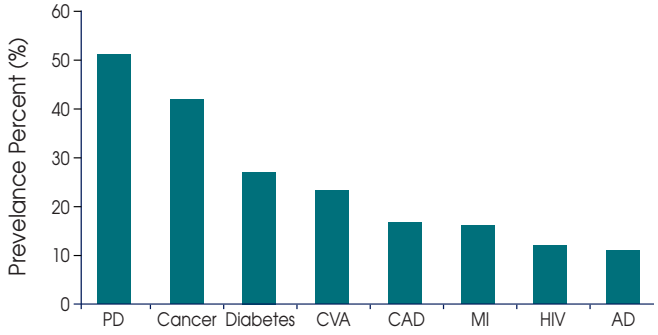
Given the above limitations, software packages do not replace the educated, astute, and conscientious prescriber who remains the major safeguard against the occurrence of serious untoward interactions. The authors hope that this guide can serve as an aid to these prescribers in providing safe and effective 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 chronic treatment and/or prevention of long-term illnesses (eg, schizophrenia and Alzheimer's disease, respectively).

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

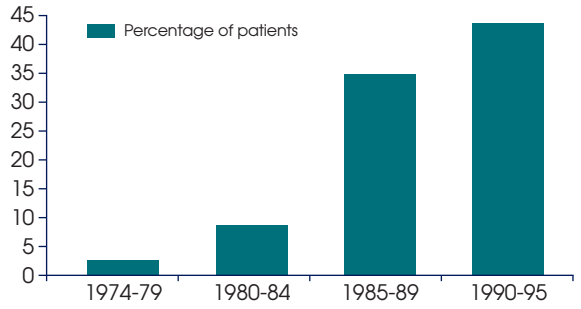
Figure 1
Prevalence of Depression in Chronic Disease[12-16]



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

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Figure 2
Increasing Use of Polypharmacy*at the NIMH Biological Psychiatry Branch Between 1974 and 1995[25]



*≥3 medications at the time of discharge.
NIMH=National Institute of Mental Health.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Figure 3
How Knowledge of CYP Enzymes Will Simplify Understanding of Pharmacokinetic Interactions[3,32]

Drug A affects* → CYP enzyme X

CYP enzyme X metabolizes → B, C, D, E

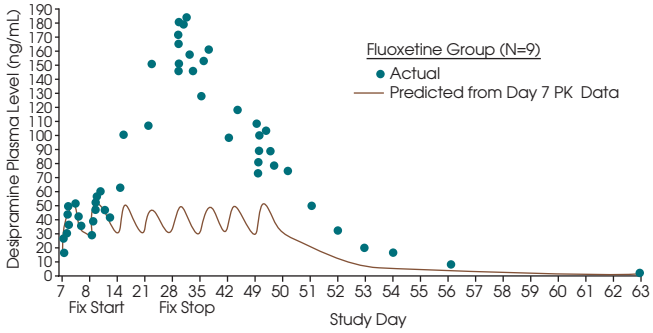
Therefore, Drug A affects* → B, C, D, E

*Could be inhibition or induction
CYP=cytochrome P450.

Preskorn SH. *Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors*. 1st ed. Caddo, Ok: Professional Communications, Inc; 1996:234-236. Reprinted with permission. ©Preskorn.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Figure 4
Time Course: Effect of Fluoxetine on CYP 2D6 Function Using Desipramine as the Probe Drug[47]



CYP=cytochrome P450; PK=pharmacokinetics; Flx=Fluoxetine.

Preskorn SH, Alderman J, Chung M, Harrison W, Messig M, Harris S. Pharmacokinetics of desipramine co-administered with sertraline orfluoxetine. *J Clin Psychopharmacol*. 1994;2:90-98. Adapted with permission. ©Preskorn.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Table 1
What Percentage of Patients on Antidepressants Have the Potential to Experience a DDI as a Function of Treatment Setting?[3,9,11]

Clinical Setting	Number of Patients	Only on Antidepressants (%)	On Antidepressants and ≥3 Other Medications (%)
Primary care	2,045	28	34
Psychiatry clinic	224	29	30
VA Medical Center and clinics	1,076	7	68
HIV clinic	66	2	77

DDI=drug drug interaction; VA=Veterans Administration; HIV=human immunodeficiency virus.

Preskorn SH. *Outpatient Management of Depression: A Guide for the Practitioner*. Caddo, Ok: Professional Communications, Inc; 1999. Reprinted with permission. ©Preskorn.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Table 2
The "AVOID" Method for Assessment of Current Medications

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?

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Table 3
Personal Formulary: Essential Elements of Knowledge for Each Drug

Dosage Forms
- Know the dosage forms available for the drugs posted

Pharmacokinetic Data
- Enzymes or transporters responsible for elimination
- Half-life and effect of renal or liver disease
- Pharmacokinetic variability in ethnic groups

Pharmacodynamic Data
- Receptor affinity and specificity relative to other drugs
- Clinically important side effects

Clinical Trial data
- An ongoing familiarity with all major clinical trials and studies

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Table 4
Examples of SSRIs With Different Brand Names Throughout the World[32]

Country	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Argentina	NA	Animex-On, Equilibrane, Foxetin, Neupax, Saurat	NA	Aropax	Zoloft
Australia	NA	Prozac 20	NA	Aropax	Zoloft
Austria	Seropram	Fluctine	Floxyfral	Seroxat	Tresleen
Belgium	Cipramil	Prozac	Floxyfal	Aropax, Seroxat	Zoloft
Canada	NA	Prozac	Luvox	Paxil	Zoloft
Denmark	Cipramil	Fontex, Fonzac	Fevarin	Seroxat	Zoloft
Finland	Cipramil	Fontex, Fonzac	Fevarin	Seroxat	Zoloft
France	Cipramil	Prozac	Floxyfral	Deroxat	Zoloft
Germany	Saroten	Fluctin	Fevarin	Seroxat, Tagonis	Zoloft
Greece	Seropram	Flonital, Fluxadir Ladose, Orthon	Dumyrox	Seroxat	NA
Italy	NA	Fluxeren, Prozac	Dumirox, Fevarin, Maveral	Sereupin, Seroxat	Serad, Tatig, Zoloft
Mexico	NA	Fluoxac, Prozac	NA	Aropax, Paxil	Altruline
Netherlands	NA	Prozac	Fevarin	Seroxat	Zoloft
Norway	Cipramil	Fontex	Fevarin	Seroxat	Zoloft
Portugal	NA	Digassim, Nodepe, Prozac, Psipax, Tuneluz	Dumyrox	NA	NA
South Africa	Cipramil	Prozac	Luvox	Aropax 20	Zoloft
Spain	NA	Adofen, Prozac, Reneuron	Dumirox	Frosinor, Motivan, Seroxat	Aramis, Besitran
Sweden	Cipramil	NA	Fevarin	Seroxat	Zoloft
Switzerland	Seropram	Fluctine	Floxyfral	Deroxat	Gladem, Zoloft
Turkey	NA	Depreks, Prozac	Faverin	NA	Lustral
United Kingdom	NA	Prozac	Faverin	NA	Lustral
United States	Celexa	Prozac	Luvox	Paxil	Zoloft

SSRIs=selective serotonin reuptake inhibitors; NA=not available at the time of original publication.

Preskorn SH. *Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors.* 1st ed. Caddo, Ok: Professional Communications, Inc; 1996:234-236. Adapted with permission. ©Preskorn.

Preskorn SH, Flockhart D. *Primary Psychiatry*. Vol 11, No 2. 2004.

Table 5
Classification of Neuropsychiatric Medications Based on Their Principle Mechanism of Action[33]

Acetylcholine

Muscarinic Acetylcholine Receptor Antagonism

Atropine
Belladonna
Benztropine (Cogentin)
Biperiden (Akineton)
Clidinium (Quarzan)
Dicyclomine (eg, Bentyl)
Glycopyrrolate (eg, Robinul)
Mepenzolate (Cantil)
Methscopolamine (Pamine)
Orphenadrine (eg, Norflex)
Oxybutynin (eg, Ditropan)
Procyclidine (Kemadrin)
Propanthethine (eg, Pro-Banthine)
Scopolamine (eg, Sopace)
Trihexyphenidyl (Artane)

Also includes: a number of low-potency phenothiazines (see the class labeled "5-HT_{2A}, D_2, and Multiple Other Receptor Antagonism"), a number of tertiary amine TCAs and related antidepressants (see the class labeled "Dual Norepinephrine and Serotonin (NE >5-HT) Uptake Pump Inhibition Plus Other Actions"), clozapine, olanzapine, and protriptyline.

Table 5 (cont)
Classification of Neuropsychiatric Medications Based on Their Principle Mechanism of Action[33]

Cholinesterase Inhibition
Donepezil (Aricept) | Galantamine (Reminyl) | Rivastigmine (Exelon)

Biogenine Amines (Effects on NE, D, 5-HT)
Catechol-O-methyltransferase Inhibition
Entacapone (Comtan) | Tolcapone (Tasmar)

Monoamine Oxidase Inhibition
Isocarboxazid (Marplan) | Selegiline (Eldepryl) | Tranylcypromine (Parnate)
Phenelzine (Nardil)

Biogenic Amine Release
Amphetamines | Dextroamphetamine (eg, Dexedrine) | Methylphenidate (eg, Ritalin)
Benzphetamine (Didrex) | Diethylpropion (eg, Tenuate) | Phendimetrazine (eg, Prelu-2)
Bupropion (Wellbutrin, Zyban)* | Methamphetamine (eg, Desoxyn) | Phentermine (eg, Ionamin)
Classically NE>D>5-HT, but rank order of effects on these neurotransmitters may vary amongst the different drugs in this class.

Dopamine
Dopamine Agonism (General)
Levodopa (dopamine precursor, component of Sinemet)

D_2 Agonism
Bromocriptine (+ partial D_1 agonism) (Parlodel) | Pramipexole (+ D_3 agonism but no D_1 activity) (Mirapex)
Pergolide (+ D_1 agonism) (Permax) | Ropinirole (+ D_3 agonism but no D_1 activity) (Requip)

Uptake Inhibition
Amantadine (Symmetrel) | Cocaine

Dopa Decarboxylase Inhibitors
Carbidopa (component of Sinemet)

Selective D_2 Receptor Antagonism
Fluphenazine (eg, Prolixin)† | Pimozide (Orap) | Trifluoperazine (eg, Stelazine)
Haloperidol (eg, Haldol)‡ | Piperazine (Entacyl)
Perphenazine (eg, Trilafon)

D_2 Receptor Partial Agonism
Aripiprazole (Abilify)‡

D_2 Receptor Antagonism Plus Multiple Other Effects
See class labeled "5-HT_{2A}, D_2, and 5-HT_{2A}, D_2, and Multiple Other Receptor Antagonism."

Ethanol
Solubilizes electrically excitable membranes

GABA
Barbiturates (enhance the binding of GABA to $GABA_A$ receptors and promote rather than displace the binding of benzodiazepines)
Amobarbital (Amytal) | Betharbital | Primidone (Mysoline)
Butabital (eg, Butisol) | Pentobarbital (eg, Nembutal) | Secobarbital (Seconal)

Barbiturate-Like Drugs
Chloral hydrate (eg, Aquachloral) | Ethchlorvynol (Placidyl)

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

Table 5 (cont)
Classification of Neuropsychiatric Medications Based on Their Principle Mechanism of Action[33]

Benzodiazepine-Like Drugs
Meprobamate (eg, Miltown)

GABA Transaminase Inhibition and Stimulation of Glutaminic Acid Decarboxylase
Divalproex sodium (Depakote) | Valproic acid (Depakene) | Valproate sodium (Depacon)

Promotion of Nonvesicular Release of GABA
Gabapentin (Neurontin)

Herbals
Ginkgo biloba | Ginseng | St. John's wort

Histamine
Centrally Active H_1 Antagonism
Chlorpheniramine | Ciphenhydramine (Benadryl) | Hydroxyzine (Atarax)
Cyclobenezaprine (Flexeril)
Also includes: a number of low-potency phenothiazines (see the class labeled "5-HT_{2A}, D_2, and Multiple Other Receptor Antagonism"), a number of tertiary amine tricyclic and related antidepressants (see the class labeled "Dual Norepinephrine and Serotonin (NE >5-HT) Uptake Pump Inhibition Plus Other Actions"), clozapine, olanzapine, maprotiline, mirtazapine, nefazodone, and quetiapine.

Ion Channel Inhibition

Carbamazepine (eg, Tegretol)	slows the recovery of voltage-activated Na^+ channels
Dantrolene (Dantrium)	interferes with the release of Ca^{++} from sacroplasmic reticulum
Felbamate (Felbatol)	inhibits N-methyl-D-aspartate–evoked responses and potentiates GABA-evoked responses
Lithium (eg, Eskalith)	substitutes for multiple ions
Lamotrigine (Lamictal)	see carbamazapine plus inhibition of glutamate release
Mephentyoin (Mesantonin)	slows recovery of voltage-activated Na^+ channels
Phentyoin (eg, Dilantin)	slows recovery of voltage-activated Na^+ channels
Topiramate (Topamax)	reduces voltage-gated Na^+ currents, enhances postsynaptic $GABA_A$ 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 labeled "5-HT_{2A} and D_2 Antagonists With Other Effects"), a number of tertiary amine tricyclic and related antidepressants (see the class labeled "Serotonin and Norepinephrine Reuptake Inhibition With Other Effects"), clozapine, pimozide, and ziprasidone. Thioridazine has a black box warning, possibly because of such effects.

Norepinephrine
α_1 Antagonism
This mechanism is not known to mediate any desired CNS effect, thus no neuropsychiatric medications were developed to have this specific mechanism of action. Nevertheless, several neuropsychiatric medications do achieve concentrations under clinically relevant dosing conditions, which block this receptor. These medications include: amitriptyline, chlorpromazine, clozapine, quetiapine, nefazodone, risperidone, thioridazine, and trazodone.

α_2 Agonism
Clonidine (eg, Catapres)

Uptake Pump Inhibition
Atomoxetine (Strattera) | Maprotoline (eg, Ludiomil)* | Protriptyline (eg, Vivactil)*
Cocaine | Nortriptyline (eg, Pamelor)* | Reboxetine (Vespar)*§
Desipramine (eg, Norpramin)* | Phentermine (eg, Ionamine)

Dual Norepinephrine and Serotonin (NE >5-HT) Uptake Pump Inhibition Plus Other Actions
Amitriptyline (eg, Elavil)* | Clomipramine (eg, Anafril)* | Imipramine (eg, Tofranil)*
Amoxapine (eg, Ascendin)* | Doxepin (eg, Sinequan)* | Trimipramine (eg, Surmontil)*

Opiate Receptor
Alfentanil (Alfental) | Hydromorphine (eg, Dilaudid) | Oxycodone (Roxicodone)
Buprenorphine (Buprenex) | Meperidine (eg, Demerol) | Pentazocine (eg, Talwin)
Codeine | Methadone (eg, Dolophine) | Prophyphene (eg, Darvon)
Fentanyl (eg, Sublimaze) | Nalbuphine (eg, Nubain) | Tramadol (Ultram)
Hydrocodone (eg, Vicodin) | Opium (eg, Paregoric)

Serotonin
5-HT_{1A} Partial Agonism

Table 5 (cont)
Classification of Neuropsychiatric Medications Based on Their Principle Mechanism of Action[33]

Buspirone (eg, Buspirone)

5-HT$_{1B/D}$ Agonism

Ergotamine (eg, Ergomar)
Dihyrdoergotamine (D.H.E. 45)
Naratriptan (Amege)
Sumitriptan (Imitrex)
Rizatriptan (Maxalt)
Zolmitriptan (Zomig)

5-HT$_2$ Receptor Antagonism

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

5-HT$_{2A}$ and D$_2$ Receptor Antagonism

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

5-HT$_{2A}$, D$_2$, and Multiple Other Receptor Antagonism

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

Serotonin Uptake Inhibition

Dexfenfluramine (Redux)
Fenfluramine (Pondimin)
Fluvoxamine (eg, Luvox)
Paroxetine (Paxil)

Selective Serotonin Uptake Inhibition

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

Dual Serotonin and Norepinephrine (5-HT>NE) Uptake Pump Inhibition

Sibutramine (Meridia)
Venlafaxine (Effexor)*

* See Table 8 for relative effects on neuroreceptors.
† See Table 7 for relative effects on neuroreceptors.
‡ See Table 6 for relative effects on neuroreceptors.
§ Not available in the United States.

5-HT=serotonin; D=dopamine; NE=norepinephrine; TCAs=trycyclic antidepressants; GABA=γ-aminobutyric acid; Na=sodium; Ca=calcium; H=histamine; CNS=central nervous system.

Preskorn SH. Classification of neuropsychiatric medications by principle mechanism of action: a meaningful way to anticipate pharmacodynamically mediated drug interactions. *J Psychiatr Pract.* 2003;5:376-383. Reprinted with permission. ©Preskorn.
Preskorn SH, Flockhart D. *Primary Psychiatry.* Vol 11, No 2. 2004.

Table 6
Relative Binding Affinity* of Selected Antipsychotics for Specific Neuroreceptors†[33,34,51-54]

Agent	D$_1$	D$_2$	D$_3$	D$_4$	5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_{2C}$	α$_1$	H$_1$	M$_1$
Aripiprazole	780	1‡	2	129	5	10	44	138	180	>1,000
Clozapine	45	66	250	18	460	8	8	4	3	1
Haloperidol	300	1	3	4	>1,000	64	>10,000	9	629	>2,000
Olanzapine	16	6	25	24	>5,000	2	12	9	4	1
Quetiapine	65	23	49	230	400	42	214	1	2	17
Risperidone	614	6	14	13	300	1	36	1	29	>10,000
Ziprasidone	>1,000	13	18	80	8	1	2.5	28	125	>1,000

* Relative binding affinity= $\frac{\text{binding affinity for secondary sites of action}}{\text{binding affinity for most potent site of action}}$

† In this table, the most potent site of action for a specific drug is arbitrarily given a value of 1 so that the drug's affinity for all other sites can be expressed in relationship to its most potent site of action. The actual affinity in nanomolar concentration for its most potent site of action for each of the drugs listed above are as follows: aripiprazole D$_2$ (0.34), clozapine M$_1$ (1.9), haloperidol D$_2$ (0.7), olanzapine M$_1$ (1.9), quetiapine α$_1$ (7), risperidone α$_1$ (0.7), ziprasidone 5-HT$_{2A}$ (0.7).

‡ Partial agonist at D$_2$ receptor where others in this table are full antagonists.

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

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Table 7

Relative Binding Affinity* of Selected Antipsychotics for Specific Neuroreceptors†[33,34,51-54]

Agent	D_2	5-HT_{2A}	α_1	α_2	H_1	M_1
Chlorpromazine	13	1	2	546	6	50
Cis-Thiothixene	1	289	24	444	13	>1,000
Fluphenazine	1	24	11	>1,000	26	>1,000
Loxapine	12	1	20	>1,000	4	331
Thioridazine	5	4	1	167	3	3

* Relative binding affinity = $\frac{\text{binding affinity for secondary sites of action}}{\text{binding affinity for most potent site of action}}$

† In this table, the most potent site of action for a specific drug is arbitrarily given a value of 1 so that the drug's affinity for all other sites can be expressed in relationship to its most potent site of action. The actual affinity in nanomolar concentration for its most potent site of action for each of the drugs listed above are as follows: chlorpromazine 5-HT_{2A} (1.41), cis-thiothixenc D_2 (0.45), fluphenazine D_2 (0.8), loxapine 5-HT_{2A} (1.37), thioridazine α_1 (5).

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

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Table 8

Relative Binding Affinity* of Specific Antidepressants to Specific Neurotransporters and Neuroreceptors†[33,55,56]

	SET	NET	DAT	H_1	M_1	α_1	α_2	D_2	5-HT_{2A}
Tertiary amine TCAs									
Amitriptyline	4	34	>1,000	1	16	25	827	910	27
Amoxapine	57	16	>1,000	24	970	49	>1,000	17	1
Chlorimipramine	1	133	>1,000	113	133	138	>1,000	679	97
Doxepin	280	124	>1,000	1	350	100	>1,000	>1,000	105
Imipramine	1	26	>1,000	8	65	65	>1,000	>1,000	55
Trimipramine	552	>1,000	>1,000	1	218	88	>1,000	661	119
Secondary Amine TCAs									
Desipramine	21	1	>1,000	132	235	156	>1,000	>1,000	333
Maprotiline	>1,000	6	500	1	278	45	>1,000	172	60
Nortriptyline	4	1	261	2	34	14	575	277	10
Protriptyline	14	1	>1,000	18	18	92	>1,000	>1,000	47
SSRIs									
Citalopram	1	>1,000	>1,000	410	>1,000	>1,000	>1,000	NA	>1,000
Escitalopram	1	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000	NA	NA
Fluoxetine	1	293	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000	250
Fluvoxamine	1	584	>1,000	>1,000	>1,000	>1,000	>1,000	NA	>1,000
Paroxetine	1	320	>1,000	>1,000	860	>1,000	>1,000	>1,000	>1,000
Sertraline	1	>1,000	85	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000
SNRIs									
Milnacipran	1	9	>1,000	>1,000	>1,000	>1,000	NA	NA	917
Reboxetine	8	1	>1,000	44	933	>1,000	NA	NA	875
Venlafaxine	1	117	991	>1,000	>1,000	>1,000	>1,000	>1,000	>1,000
5-HT_{2A} Inhibition and Weak Serotonin									
Nefazodone	60	107	107	6	>1,000	8	>1,000	273	1
Trazodone	21	>1,000	929	45	>1,000	5	65	500	1
Specific Histamine, Serotonin, and Norepinephrine Receptor Antagonist									
Mirtazapine	>1,000	>1,000	>1,000	1	>1,000	>1,000	986	>1,000	115
Dopamine and Norepinephrine Reuptake Inhibition									
Bupropion	17	100	1	13	90	9	158	396	173

* Relative binding affinity = $\frac{\text{binding affinity for secondary sites of action}}{\text{binding affinity for most potent site of action}}$

† In this table, the most potent site of action for a specific drug is arbitrarily given a value of 1 so that the drug's affinity for all other sites can be expressed in relationship to its most potent site of action. The actual affinity in nanomolar concentration for its most potent site of action for each of the drugs listed above are as follows: amitriptyline H (1), amoxapine 5-HT_2 (1), bupropion (526), citalopram SET (1.16), chlorimipramine SET (0.28), desipramine NET (0.83), doxepin H (0.24), fluoxetine SET (0.83), fluvoxamine SET (2.22), imipramine SET (1.41), maprotiline H_1 (2), milnacipran SET (9), mirtazapine H_1 (0.14), nefazodone 5-HT_{2A} (3.33), nortriptyline NET (4.35), paroxetine SET (0.13), protriptyline NET (1.41), reboxetine NET (7), sertraline SET (0.29), trazodone 5-HT_{2A} (7.7), trimipramine H_1 (0.27), venlafaxine SET (9.1).

SET=serotonin transporter; NET=norepinephrine transporter; H=histamine; M=muscarine; D=dopamine; 5-HT=serotonin; TCAs=tricyclic antidepressants; SSRIs=selective serotonin reuptake inhibitors; NA=not available; SNRIs=selective norepinephrine reuptake inhibitors.

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Table 9
Five Reasons for Polypharmacy[3,36]

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

Preskorn SH, Lacey R. Polypharmacy: When is it rational? *J Pract Psychiatr Behav Health.* 1995;1:92-98. Reprinted with permission. ©Preskorn.

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Table 10
Parkinson's Disease as a Model of Rational Copharmacy[3,36]

Treatment	Effect (Type of Interaction)
L-Dopa	Increase synthesis of central dopamine (PK)
L-Dopa+carbidopa (Sinemet)	Carbidopa inhibits peripheral decarboxylase to reduce the dose of L-dopa needed to increase synthesis of central dopamine (PK)
L-Dopa/carbidopa+dopamine reuptake inhibitor (eg, bupropion, amantadine)	Second drug potentiates the effect of released central dopamine (PK)
L-Dopa/cardibopa+L-deprenyl	L-deprenyl increases synthesis of central dopamine and block its degradation (PK)
L-Dopa/carbidopa+bromocriptine	Bromocriptine and related D_2 agonists potentiate central dopamine agonism by addition of direct dopamine agonist (PD)

PK=pharmacokinetic; PD=pharmacodynamic; D=dopamine.

Preskorn SH, Lacey R. Polypharmacy: When is it rational? *J Pract Psychiatr Behav Health.* 1995;1:92-98. Reprinted with permission. ©Preskorn.

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Table 11
Criteria for Rational Copharmacy in Psychiatry[3,36]

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 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

Preskorn SH, Lacey R. Polypharmacy: When is it rational? *J Pract Psychiatr Behav Health.* 1995;1:92-98. Reprinted with permission. ©Preskorn.

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Table 12
Complexity of the Human Brain[45]

- 10–20 billion cells
- 75 known neurotransmitters
- 300 putative neurotransmitters
- Enzymes (synthesis, degradation)
- 2–17 receptor subtypes
- Transport mechanisms, storage and release
- Second messenger systems
- Ion channels

Preskorn SH. The human genome project and drug discovery in psychiatry: identifying novel targets. *J Psychiatr Pract.* 2001;2:133-140. ©Preskorn.

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Table 13
Summary of Major Principles to Avoid Adverse Drug-Drug Interactions*

- Be aware and follow good clinical practice
- 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
- Anticipation and prevention
  - -highly potent inducer/inhibitor
  - -narrow therapeutic index of victim
- When possible, choose low-risk perpetrators
- When possible, choose victims with multiple parallel pathways

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

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Table 14
Major Pharmacodynamic Drug-Drug Interactions Based on Mechanism of Action[51]

Acetylcholine

Muscarinic Acetylcholine Receptor Antagonism
- Mitigates and can even fully reverse the extrapyramidal symptoms caused by excessive D_2 blockade
- Can block the memory-enhancing effects of cholinesterase inhibitors in dementing illnesses, such as Alzheimer's disease
- Decreases gastric empyting, thus decreasing the absorption of acetaminophen

Cholinesterase Inhibition
- Opposite consequences to muscarinic acetylcholine receptor antagonism (see above)

Biogenine Amine (Effects on D, NE, and 5-HT)

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

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

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

Dopamine

Dopamine Agonism (General)
- Can ameliorate Parkinson's disease
- Can cause dyskinesia, hyperactivity, hyperkinesia, and psychosis
- Above effects can be augmented by other dopamine agonists and blocked by dopamine antagonists

D_2 Agonism
- Can ameliorate Parkinson's disease
- Can cause dyskinesia, hyperactivity, hyperkinesia, and psychosis
- Can aggravate dyskinesias in conditions such as Huntington's disease
- Above effects can be augmented by other dopamine agonists and blocked by dopamine antagonists

Uptake Inhibition
- Can ameliorate Parkinson's disease
- Can cause dyskinesia, hyperactivity, hyperkinesia, and psychosis
- Above effects can be augmented by other dopamine agonists and blocked by dopamine antagonists

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

Selective D_2 Receptor Antagonism
- Can cause extrapyramidal symptoms, 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 dopamine agonists

Table 14 (cont)
Major Pharmacodynamic Drug-Drug Interactions Based on Mechanism of Action[51]

D_2 Receptor Partial Agonism
- Reduced risk of extrapyramidal symptoms, 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 dopamine agonists

Ethanol

The central nervous system 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_1 receptors, and opiates.

GABA

Barbiturates
Barbiturate-Like Drugs
Benzodiazepine Binding Site Agonism
Benzodiazepine-Like Drugs
GABA Transaminase Inhibition and Stimulation of Glutaminic Acid Decarboxylase
Promotion of Nonvesicular Release of GABA
The central nervous system impairment caused by the above direct and indirect GABA agonists can be enhanced by each other and by a number of different mechanistic classes of drugs including drugs which block central H_1 receptors, ethanol, and opiates.

Histamine

Central Active H_1 Antagonism
The sedation caused by central H_1 antagonism can be amplified by:
- Drugs that promote GABA in the brain
- Ethanol
- Opiates

Ion Channel Inhibition

- There is a concern that the 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 interactions have not been formally tested with psychiatric medications due to the potential risk involved but have led in some instances to class labeling warning against such combined use principally on the basis of the theoretical concern.

Norepinephrine

α_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 α_2 agonists, angiotension-converting enzyme inhibitors, β-blockers, calcium channel inhibitors, and diuretics.

α_2 Agonism
- This mechanism decreases central NE 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 α_2 antagonist can cause clinically serious hypertensive rebound. Mirtazapine is an α_2-adrenegic antagonist.
- By decreasing NE outflow, α_2-adrenergic agonists would be expected to antagonize the effects of neuropsychiatric medications that block NE uptake pumps and MAOIs.

Norepinephrine Uptake Pump Inhibition
- The effect of these drugs would be reduced by α_2-adrenergic agonists (eg, clonidine) and would be amplified enhanced by α_2-adrenergic antagonists (eg, mirtazapine).
- This mechanism can cause generally modest blood pressure elevations through enhancing sympathetic vascular tone. This effect would modestly antagonize the effects of a variety of blood pressure lowering agents.
- This mechanism can amplify the effect of MAOIs by increasing the duration of NE in the synaptic cleft while the MAOIs increase the intracytoplasmic stores of NE available for release when the adrenergic neurons fire.

Table 14 (cont)
Major Pharmacodynamic Drug-Drug Interactions Based on Mechanism of Action[51]

Norepinephrine and Serotonin (NE>5-HT) Uptake Pump Inhibition
- These drugs carry with them the potential for combined interactions associated with either of these 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 of specific uptake inhibition that is achieved.

Dual Norepinephrine and Serotonin (NE>5-HT) 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 central nervous system arousal, particularly respiratory depression, caused by opiates can be amplified by:
- Drugs which promote GABA in the brain
- Drugs which block central H_1 receptors

Serotonin

5-HT_{1A} Partial Agonism
The pharmacology of these drugs is complicated. These receptors exist both presynaptically and postsynaptically. Presynaptically, they are analogous to the α_2-adrenergic receptor as a feedback mechanism. Postsynaptically, they serve an effector mechanism. In addition, the effect of these drugs is dependent on the intrasynaptic concentration of serotonin. At low concentrations, they act as a 5-HT_{1A} agonist to diminish serotonin outflow. At high serotonin concentrations, they act as a 5-HT_{1A} antagonist. Thus, they can theoretically interact in complex and even paradoxical ways with other serotonin active drugs. They can therefore:
- 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 was not supportive of this concept.
- For the same reason, there is a theoretical risk of serotonin syndrome when combined with serotonin uptake pump inhibitors and/or MAOIs.

5-$HT_{1B/D}$ Agonism
- There is a theoretical risk of serotonin syndrome when combined with other serotonin agonists, such as serotonin uptake pump inhibitors and MAOIs but little journal data to support this concern.

5-HT_2 Receptor Antagonism
- Serotonin agonism at this receptor may be responsible for the disruption of sleep that can be caused by serotonin uptake pump inhibitors. Trazodone blocks this receptor and is commonly used to treat the insomnia associated with serotonin uptake pump inhibitors.

5-HT_{2A} and D_2 Receptor Antagonism
- These drugs have the potential for interactions mediated by either of these mechanisms.

5-HT_{2A}, D_2, and Multiple Other Receptor Antagonism
- These drugs have the potential for interactions mediated by all of these mechanisms.

Serotonin Uptake Inhibition
- The effects of these drugs can be substantially amplified by MAOIs up to and including fulminant and fatal serotonin syndromes. Serotonin syndrome is a theorectical risk when combined with 5-HT_{1A} partial agonists and 5-$HT_{1B/D}$ agonists.
- Lithium, by facilitating the neuronal release of serotonin, can enhance the serotonin 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 "Serotonin Uptake Inhibition"

Dual Serotonin and Norepinephrine (5-HT>NE) Uptake Pump Inhibition
See "Serotonin and Norepinephrine Uptake Pump Inhibition"

D=dopamine; NE=norepinephrine; 5-HT=serotonin; GABA=γ-aminobutyric acid; H=histamine; MAOIs=monoamine oxydase inhibitors.

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Table 15
Drugs Categorized as Specific CYP Enzyme Substrates, Inhibitors, or Inducers to Permit Prediction of CYP-Mediated Drug-Drug Interactions[2]

1A2 Substrates

Amitriptyline (Elavil, Endep)	Haloperidol (Haldol)
Clomipramine (Anafril)	Imipramine N-DeMe (Tofranil)
Clozapine (Clozaril)	Olanzapine (Zyprexa)
Cyclobenzaprine (Cyclobenz, Flexeril)	Riluzole (Rilutek)
Fluvoxamine (Luvox)	Tacrine (Cognex)
	Zolmitriptan (Zomig)

1A2 Inhibitors	*Relative Effect at Usual Therapeutic Dose*
Amiodarone (Cordarone, Pacerone)	+++
Cimetidine (Tagamet)	+
Fluoroquinolones	+
Fluvoxamine (Luvox)	+
Methoxsalen (Oxsoralen-Ultra, Uvadex)	+
Ticlopidine (Ticlid)	++

1A2 Inducers	
Broccoli	~
Brussel sprouts	~
Char-grilled meat	~
Methyl cholanthrene	~
Modafinil (Provigil)	+
Mafcillin (Nafcil, Unipen)	+
β-naphthoflavone	+
Omeprazole (Prilosec)	+
Tobacco	~

2B6 Substrates

Bupropion (Wellbutrin, Zyban)	Methadone (Dolophine)
Efavirenz (Sustiva)	

2B6 Inhibitors	*Relative Effect at Usual Therapeutic Dose*
Thiotepa (Thioplex)	+++
Ticlopidine (Ticlid)	++

2B6 Inducers	
Phenobarbital (Phenob)	++
Rifampin (Rifadin, Rifamate, Rimactane)	++

2C19 Substrates

Antiepileptics

Amitriptyline (Elavil, Endep)	R-mephobarbital (Mebaral)
Citalopram (Celexa)	Moclobemide
Clomipramine (Anafranil)	Nelfinavir (Viracept)
Diazepam (Diastat, Dizac, Valium)	Nilutamide (Niladron)
Hexobarbital	Phenobarbitone
Imipramine N-DeME (Tonfanil)	Phenytoin(O) (Dilantin)
S-mephenytoin (Mesantoin)	Primidone (Mysoline)

2C19 Inhibitors	*Relative Effect at Usual Therapeutic Dose*
Cimetidine (Tagamet)	+
Felbamate (Felbatol)	+
Fluoxetine (Prozac, Sarafem)	++
Fluvoxamine (Luvox)	+++
Indomethacin (Indocin)	+
Ketoconazole (Nizoral)	++
Lansoprazole (Prevacid)	++++
Omeprazole (Prilosec)	+++
Paroxetine (Asimia, Paxil)	+++
Probenicid (Colbenemid, Probene)	+
Ticlopidine (Ticlid)	+++
Topiramate (Topamax)	++

2C19 Inducers	*Relative Effect at Usual Therapeutic Dose*
Carbamazepine (Carbatrol, Epital, Tegretol)	++
Norethindrone (Brevicon, Norinyl, Ortho-Novum)	+
NOT pentobarbital (Nembutal, Pentobarb)	~
Prednisone (Deltasone, Liquid Pred, Orasone, Sterapred)	+
Rifampin (Rifadin, Rifamate, Rimactane)	++

2C9 Substrates

Amitriptyline (Elavil, Endep)	Phenytoin (Dilantin)
Fluoxetine (Prozac, Sarafem)	S-warfarin (Coumadin)

2C9 Inhibitors	*Relative Effect at Usual Therapeutic Dose*
Amiodarone (Cordarone, Pacerone)	+++
Fluconazole (Diflucan)	++
Fluvastatin (Lescol)	++
Fluvoxamine (Luvox)	+
Isoniazid (Rifater, Nydrazid)	+
Lovastatin (Altocor, Mevacor)	+++
Paroxetine (Paxil, Asimia)	++
Phenylbutazone	+
Probenicid (Colbenemid, Probene)	++
Sertraline (Zoloft)	+++
Sulfamethoxazole (Bactrim, Bethaprim, Cotrim, Septra, Sulfatrim, Trimeth-Sulfa, Gantanol)	+++
Sulfaphenazole	+
Teniposide (Vumon)	+++
Trimethoprim (Trimeth-Sulfa, Proloprim, Trimpex, Polytrim)	+
Zafirlukast (Accolate)	++

2C9 Inducers	
Rifampin (Rifadin, Rimactane, Rifamate)	++
Secobarbital (Seconal, Tuinal)	++

2D6 Substrates

Antidepressants

Amitriptyline (Elavil, Endep)	Imipramine (Tonfanil)
Clomipramine (Anafril)	Nortriptyline (Pamelor)
Desipramine (Norpramin)	Paroxetine (Paxil, Asimia)

Antipsychotics

Aripiprazole (Abilify)	Risperidone (Risperdal)
Haloperidol (Haldol)	Thioridazine (Mellaril)
Perphenazine (Trilafon)	

Amphetamines

Chlorpheniramine (Chlor-Trimeton, Efidac)	Methoxyamphetamine
Chlorpromazine (Thorazine)	Minaprine
Codeine	Nortriptyline (Pamelor)
Dexfenfluramine (Redux)	Quanoxan
Fluoxetine (Prozac, Sarafem)	Sparteine
Fluvoxamine (Luvox)	Tramadol (Ultram, Ultracet)
Metoclopramide (Reglan, Metoclopram)	Venlafaxine (Effexor)

Table 15 (cont)
Drugs Categorized as Specific CYP Enzyme Substrates, Inhibitors, or Inducers to Permit Prediction of CYP Mediated Drug-Drug Interactions[2]

2D6 Inhibitors

Amiodarone (Cordarone, Pacerone)	+++
Bupropion (Wellbutrin, Zyban)	+++
Celecoxib (Celbrex)	++
Chlorpromazine (Thorazine)	+++
Chlorpheniramine (Chlor-Trimeton, Efidac)	+
Cimetidine (Tagamet)	+
Citalopram (Celexa)	+
Clomipramine (Anafril)	+
Escitalopram (Lexapro)	+
Fluoxetine (Prozac, Sarafem)	+++
Red-haloperidol (Haldol)	++
Levomepromazine	++
Methadone (Dolophine)	++
Metoclopramide (Metoclopram, Reglan)	+
Mibefradil (Posicor)	+
Moclobemide (Manerix)	+
Paroxetine (Paxil, Asimia)	+++
Quinidine (Quinaglute, Cardioquin, Quinidex)	+++
Ranitidine (Tritec, Zantac)	+
Sertraline (Zoloft)	+
Terbinafine (Lamisil)	++

2E1 Substrates

Acetaminophen (Tylenol, etc)
Chlorzoxazone (Paraflex, Parafon Forte)

2E1 Inhibitors	*Relative Effect at Usual Therapeutic Dose*
Diethyl-dithiocarbamate	+++
Disulfiram (Antabuse)	+++

2E1 Inducers

Ethanol (Dehydrated alcohol)	++
Isoniazid (Nydrazid, Rifater)	++

3A4, 3A5, 3A7 Substrates

Benzodiazepines

Alprazolam (Xanax)	Midazolam (Versed)
Diazepam (Diastat, Dizac, Valium)	Triazolam (Halcion)

Antihistamines

Astemizole (Hismanal)
Chlorpheniramine (Chlor-Trimeton, Efidac)
Terfenidine (Seldane)

Miscellaneous

Alfentanyl (Alfenta)	Dextromethorphan
Aripiprazole (Abilify)	(Benylin DM, Delsym,
Buspirone (Buspar)	Touro DM, Tussi Org)
Codeine-N-demethylation	Donepezil (Aricept)

Miscellaneous (cont)

Eplerenone (Inspra)	Pimozide (Orap)
Fentanyl (Actiq, Duragesic, Sublimaze)	Quetiapine (Seroquel)
Haloperidol (Haldol)	Trazodone (Desyrel)
Methadone (Dolophine)	Zaleplon (Sonata)
Nefazodone (Serzone)	Ziprasidone (Geodon)
Ondansetron (Zofran)	(minor pathway)
O-desmethylvenlafaxine (major metabolite of venlafaxine)	Zolpidem (Ambien)

3A4,5,7 Inhibitors	*Relative Effect at Usual Therapeutic Dose*
HIV Antivirals	
Amiodarone (Cordarone, Pacerone)	+++
NOT azithromycin (Zithromax)	~
Cimetidine (Tagamet)	+++
Clarithromycin (Biaxin)	+++
Delaviridine (Rescriptor)	++
Diltiazem (Cartia, Cardizem, Dilacor, Diltiazem, Taztia, Tiamate, Tiazac)	++
Erythromycin (Emgel)	++
Fluconazole (Diflucan)	++
Fluvoxamine (Luvox)	++
Gestodene	++
Grapefruit juice	+++
Indinavir (Crixivan)	++
Itraconazole (Sporanox)	+++
Ketoconazole (Nizoral)	+++
Nefazodone (Serzone)	+++
Nelfinavir (Viracept)	++
Norfloxacin (Chibroxin, Noroxin)	+
Norfluoxetine	++
Ritonavir (Norvir)	+++
Saquinavir (Fortovase, Invirase)	+
Verapamil (Calan, Covera, Isoptin)	+++

3A4,5,7 Inducers

HIV Antivirals	
Barbiturates	++
Carbamazepine (Carbatrol, Epital, Tegretol)	++
Efavirenz (Sustiva)	++
Modafinil (Provigil)	+
Nevirapine (Viramune)	++
Phenobarbital (Phenob)	++
Phenytoin (Dilantin)	++
Rifabutin (Mycobutin)	++
Rifampin (Rifadin, Rifamate, Rimactane)	++
St. John's wort (Hypericum perforatum)	++

CYP=cytochrome P450; DDIs=drug-drug interactions; HIV=human immunodeficiency virus.
Inhibition variable: +=<2–fold increase plasma drug levels; ++=>2–4–fold; +++=>4–fold.
Induction variable: ~=usual clearance; +=<2 usual clearance; ++=>2 usual clearance

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Table 16
Potential Mechanisms Underlying Pharmacokinetic Drug-Drug Interactions[57]

- Protein binding*
- Phase I enzymes -CYPs and nonCYPs
- Phase II enzymes
- ABC transporters
- Nuclear receptors

*Although firmly entrenched in the minds of physicians, this mechanism rarely mediates clinically significantly as explained in the text.

ABC=ATP-binding casette; CYPs=cytochrome P450.

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Table 17
Limitations of Current Software Packages[3]

- May not be mechanism based
- Generally only a binary system
- 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 18
Reporting Adverse Drug Reactions

MedWatch: 1-800-FDA-1088, Fax: 1-800-FDA-0178
Report online at: www.fda.gov/medwatch
Practitioner reporting online at: www.usp.org

FDA=Food and Drug Administration.

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Appendix I
Web Sites* for Additional Information[2,3,60-64]

Description	Web site
Psychiatric Drug Interactions	http://www.preskorn.com
Cytochrome P450 Interactions	http://www.drug-interactions.com
FDA Food and Drug Interactions	http://vm.cfsan.fda.gov/~lrd/fdinter.html
Herbal Interactions	http://www.personalhealthzone.com/herbsafety.html
HIV Drug Interactions	http://www.hiv-druginteractions.org/
HIV Drug Interactions	http://www.projinf.org/fs/drugin.html
Grapefruit Juice – Drug Interactions	http://www.powernetdesign.com/grapefruit/

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

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

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Appendix II
Current Drug Drug Interactions Software Packages[65-69]

- Drug facts and comparisons
- Epocrates
- Hansten's
- Mhc.com/Cytochromes
- Micromedex

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