Med-Psych Drug-Drug Interactions Update

An Overview of Psychotropic Drug-Drug Interactions

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The psychotropic drug-drug interactions most likely to be relevant to psychiatrists' practices are examined. The metabolism and the enzymatic and P-glycoprotein inhibition/induction profiles of all antidepressants, antipsychotics, and mood stabilizers are described; all clinically meaningful drug-drug interactions between agents in these psychotropic classes, as well as with frequently encountered nonpsychotropic agents, are detailed; and information on the pharmacokinetic/pharmacodynamic results, mechanisms, and clinical consequences of these interactions is presented. Although the range of drug-drug interactions involving psychotropic agents is large, it is a finite and manageable subset of the much larger domain of all possible drug-drug interactions. Sophisticated computer programs will ultimately provide the best means of avoiding drug-drug interactions. Until these programs are developed, the best defense against drug-drug interactions is awareness and focused attention to this issue. (Psychosomatics 2005; 46:464–494)

The array of available psychopharmacologic agents has expanded tremendously over the last 20 years. The growing range of treatment options has made treating patients more complex. It is a formidable challenge to remain familiar with the evolving evidence base. Choosing appropriate agents for patients and making shrewd changes when faced with medication intolerance or treatment resistance occupy the bulk of most psychiatrists' pharmacological concerns. However, another domain of psychopharmacology is critical to best practice, and it should precede the quest for efficacy. To paraphrase Hippocrates, it is incumbent on clinicians to "First, do no harm." Unfortunately, practitioners often fall well short of that dictum, especially where drug-drug interactions are concerned.

Drug-drug interactions are actually quite commonplace[1–5] and are responsible for considerable patient morbidity and mortality.[6–8] A growing and sobering evidence base implicates drug-drug interactions as a major contributor to hospital admissions, treatment failures, avoidable medical complications, and subsequent health care costs.[4,5,9–11] Yet, drug-drug interactions are rarely foremost in the minds of otherwise excellent clinicians. This disconnection is explained, in part, by our relatively primitive ability to detect drug-drug interactions.[12,13] However, as

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understanding of the importance of drug-drug interactions grows, concerned physicians are eager to know more.

Most current drug-drug interaction software programs have problems with both sensitivity and specificity[14] and are not especially user friendly. They often promote a therapeutic paralysis that is almost as undesirable as an ignorance of drug-drug interactions. There are some excellent publications on this topic, which appropriately examine the issue of drug-drug interactions across medical disciplines.[15,16] However, for many psychiatrists, this wide range presents an overwhelming flood of information. Grappling with the entire array of drug-drug interactions is a worthwhile goal for anyone who prescribes medications, but it can be a daunting enterprise. An ideal starting point for psychiatrists is to examine drug-drug interactions involving the familiar psychotropic agents that are most relevant to their practices. This review focuses on intrapsychotropic drug-drug interactions involving antidepressants, antipsychotics, and mood stabilizers.

Types of Drug-Drug Interactions

The two major varieties of drug-drug interactions are pharmacodynamic interactions and pharmacokinetic interactions. Pharmacodynamic interactions represent the synergy or antagonism of each drug's effects at target receptors. For example, the synergistic anticholinergic activity of amitriptyline combined with benztropine can produce constipation, heat stroke, urinary retention, and other related difficulties.[17] Another familiar example is central serotonin syndrome, which results from the combination of a monoamine oxidase inhibitor (MAOI) with a selective serotonin reuptake inhibitor (SSRI).[18,19] In pharmacokinetic interactions, one agent causes the blood level of another agent to be raised or lowered. Pharmacokinetic drug-drug interactions may occur through multiple mechanisms, including alterations in drug metabolism, absorption, excretion, and distribution.

Pharmacodynamic drug-drug interactions are usually intuitively straightforward. If one has a basic sense of a drug's mechanism of action and receptor occupancies, these interactions can often be predicted and avoided. Pharmacokinetic drug-drug interactions are much more difficult to anticipate. Knowing how a drug accomplishes its intended therapeutic effect rarely confers any knowledge of its kinetic parameters or of the ways these parameters will interact with those of another drug. Most of the challenge posed by drug-drug interactions rests in the pharmacokinetic domain, which is predominantly concerned with metabolic alterations.

Metabolic Enzymes

Several key enzymatic systems are frequently involved in pharmacokinetic drug-drug interactions. The most prominent is the cytochrome P450 system. The P450 system is a family of mostly hepatic enzymes that perform oxidative (phase I) metabolism. Specific P450 enzymes are named by number-letter-number sequences; the major enzymes in this group are 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. P450 substrates are agents that are metabolized by particular P450 enzymes. For instance, nortriptyline is metabolized primarily by P450 2D6, and it is therefore a substrate of this enzyme.[20,21] P450 inhibitors impair the ability of specific P450 enzymes to metabolize their target substrates, thus producing increased blood levels of those substrates. Conversely, inducers cause an increase in the production of particular P450 enzymes, leading to increased metabolism of substrates of those P450 enzymes. Enzymatic inhibition is usually immediate, whereas induction usually requires several days to 2 or more weeks to exert a meaningful effect on drug metabolism.

A related metabolic system implicated in drug-drug interactions is phase II conjugative metabolism. The most prominent phase II enzymatic family is the uridine 5′-diphosphate glucuronosyltransferases (UGTs). Like the P450 system, UGTs are identified by a number-letter-number scheme (1A1, 1A4, 2B7, 2B15, etc.), and each enzyme has a unique array of substrates, inhibitors, and inducers. Phase I enzymes usually perform the bulk of the metabolic workload. Phase II conjugation generally serves as a metabolic capstone, rendering substances that have already undergone phase I oxidation more hydrophilic and thus more readily excretable. For this reason, the contribution of phase II metabolism to drug-drug interactions is typically not as significant as that of phase I metabolism. However, the metabolism of several agents, including lamotrigine,[22] olanzapine,[23] and many narcotic analgesics,[24,25] is handled solely or primarily by the UGTs. A familiarity with prominent UGT inhibitors and inducers is thus important in order to anticipate and prevent drug-drug interactions involving these agents.

P-Glycoproteins

Of the nonmetabolic systems that mediate pharmacokinetic drug-drug interactions, the P-glycoprotein transporter is emerging as a critically important contributor. P-glycoprotein is an ATP-dependent, extruding transporter. It resides in the plasma membrane of enterocytes that line the gut lumen, and in this location it is an important reg-

ulator of drug absorption and bioavailability. It also lines the capillaries of the blood-brain barrier, where it constitutes one of the core elements preventing various substances from gaining access to the CNS. P-glycoprotein is also found in the cells lining renal tubules. Like the P450 and UGT metabolic systems, the P-glycoprotein transporter has substrates, inhibitors, and inducers. P-glycoprotein functions by extruding substrates from the cytosol of enterocytes back into the gut lumen, or from the capillaries of the blood-brain barrier back into the bloodstream. P-glycoprotein inhibitors antagonize this process and lead to greater retention and absorption of P-glycoprotein substrates. P-glycoprotein inducers increase the amount of active P-glycoprotein and thus lead to more extrusion and excretion of P-glycoprotein substrates. The net effect of this activity is that P-glycoprotein inhibitors increase the blood levels of P-glycoprotein substrates, and P-glycoprotein inducers decrease the levels of P-glycoprotein substrates. The list of known P-glycoprotein substrates, inhibitors, and inducers is already quite large and is growing with each passing month.

Other Pharmacokinetic Processes

Other pharmacokinetic drug-drug interactions are caused by alterations in absorption (not relating to P-glycoprotein), excretion, and distribution. Alterations in gastrointestinal pH, the presence or absence of food, and the rate of bowel motility are only a few of the factors that can affect absorption. For instance, the absorption of ziprasidone is much greater when it is consumed with food.[26] Drugs that affect renal excretion can alter the blood level of lithium.[27,28] Distribution issues are actually somewhat infrequent for psychotropics, although the blood level of unbound or free valproate can be significantly increased by daily antipyretic doses of aspirin.[29,30]

Current Practical Resources

Tables of drug-drug interactions involving the P450, UGT, and P-glycoprotein systems are available from multiple published and online sources. An exhaustive set of P450 tables may be found in the *Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-Glycoproteins*, by Kelly Cozza, M.D., Scott Armstrong, M.D., and Jessica Oesterheld, M.D (American Psychiatric Publishing, Inc., 2003). David Flockhart, M.D., provides an excellent P450 table online at http://medicine.iupui.edu/flockhart/. Dr. Oesterheld is the coauthor of a website, www.mhc.com/Cytochromes, which contains a P450 table tailored for psychiatrists, as well as very complete UGT and P-glycoprotein tables.

Specific Pharmacokinetic Features of Psychotropic Agents

Antidepressants

SSRIs

Citalopram Citalopram is metabolized primarily by P450 2C19, 2D6, and3A4.[31–33] It is likely a mild to moderate inhibitor of 2D6,[31,34] as evidenced by its ability to increase blood levels of desipramine and metoprolol.[35] Citalopram is a substrate of P-glycoprotein.[36]

Escitalopram The pharmacokinetic features of escitalopram are basically the same as those of citalopram.[37,38]

Fluoxetine (norfluoxetine) Fluoxetine and its active metabolite norfluoxetine are together metabolized by P450 2C9, 2C19, 2D6, and 3A4.[15,39] Together, they potently inhibit 2D6[34,40] and mildly to moderately inhibit 1A2, 2B6, 2C9, 2C19, and 3A4.[41–46] Fluoxetine can reasonably be considered a P450 pan-inhibitor, much like cimetidine. It is also a P-glycoprotein inhibitor.[47]

Fluvoxamine Fluvoxamine is primarily metabolized by P450 1A2 and secondarily by 2D6.[48,49] It is a pan-inhibitor like fluoxetine. It is a potent inhibitor of 1A2 and 2C19,[45,48,50] and a mild to moderate inhibitor of 2B6, 2C9, 2D6, and 3A4.[34,42,43,45,50,51] It is also both a substrate and an inhibitor of P-glycoprotein.[47,52]

Paroxetine Paroxetine is primarily metabolized by P450 2D6 and secondarily by 3A4.[45,53] It is a potent inhibitor of 2B6 and 2D6[34,42,54,55] but only a mild inhibitor of other P450 enzymes.[41,44] It is also both a substrate and an inhibitor of P-glycoprotein.[47]

Sertraline Sertraline and its mildly active metabolite desmethylsertraline are substrates of multiple P450 enzymes.[56,57] Sertraline inhibits 2D6 in a dose-dependent manner. At doses under 100 mg/day, sertraline may only mildly inhibit 2D6. At doses above 150 mg/day, 2D6 inhibition may become moderate to potent.[34,58] Sertraline is also a moderate inhibitor of 2B6 and 2C19[42,44] and a mild inhibitor of 1A2 and 3A4.[41,59–61] Possibly unique among the SSRIs, sertraline also appears to be a specific and potent inhibitor of UGT 1A4, as evidenced by the ability of 25

mg/day of sertraline to double the blood level of lamotrigine.[62] Sertraline is also a P-glycoprotein inhibitor.[47]

Tricyclic Antidepressants

Secondary amine tricyclic antidepressants Secondary amine tricyclic antidepressants (TCAs), including desipramine, nortriptyline, and protriptyline, are primarily substrates of P450 2D6, which performs hydroxylation on these compounds.[20,21,63–66] They are also moderate 2D6 inhibitors.[34,67,68] These TCAs also appear to be inhibitors of P-glycoprotein, and nortriptyline has been demonstrated to be a P-glycoprotein substrate.[69–72]

Tertiary amine TCAs The metabolism of tertiary amine TCAs, including amitriptyline, clomipramine, trimipramine, imipramine, and doxepin, is much more complex than that of the secondary amine TCAs. Tertiary amine TCAs undergo both demethylation to secondary amine TCAs through the action of 1A2, 2C19, and 3A4 and hydroxylation by 2D6.[63,65,73–77] UGT 1A4 also makes a minor contribution to the metabolism of tertiary amine TCAs.[23,78,79] Tertiary amine TCA inhibition of 2D6, considered without the contribution of the secondary amine metabolites, tends to be only mild, and there is some evidence that amitriptyline and imipramine are mild inhibitors of 2C19.[68] These TCAs also appear to be both substrates and inhibitors of P-glycoprotein.[69–71,80,81]

Other Antidepressants

Bupropion Bupropion is primarily metabolized by P450 2B6.[82,83] It is a moderate to potent inhibitor of 2D6.[84,85]

Duloxetine Duloxetine is metabolized by P450 1A2 and 2D6.[37,86] It is a moderate inhibitor of 2D6.[86,87]

Mirtazapine Mirtazepine has multiple metabolic pathways, including metabolism by P450 1A2, 2D6, and 3A4.[88,89] It has no significant inhibitory or inductive capabilities.[90]

MAOIs Phenelzine is a substrate of monamine oxidase A (MAOA) and lacks any significant P450 inhibitory or inductive capabilities.[18,91] Tranylcypromine is also a substrate of MAOA,[91] but it is also a potent inhibitor of P450 2A6[92,93] (a minor P450 enzyme) and a mild to moderate inhibitor of 1A2, 2C19, and 2E1.[19,94]

Nefazodone Nefazodone is primarily metabolized by P450 3A4 into three major metabolites.[95] One of these is metachlorophenylpiperazine (mCPP),[96] an acutely anxiogenic, partial serotonin agonist that relies on 2D6 for its metabolism.[97–99] Nefazodone is a potent inhibitor of 3A4.[46,100] Also, it is initially an acute inhibitor and later a chronic inducer, of P-glycoprotein.[101]

Trazodone Like nefazodone, trazodone relies primarily on P450 3A4 for its metabolism, and one of the principle metabolites resulting from its metabolism by 3A4 is mCPP.[102] Trazadone is also an inducer of P-glycoprotein.[101]

Venlafaxine Venlafaxine's metabolism relies primarily on P450 2D6, and it is a mild 2D6 inhibitor.[67] It is also both a substrate and a mild inhibitor of P-glycoprotein.[47]

Antipsychotics

Typical Antipsychotics

Phenothiazines As a general rule, phenothiazines are metabolized primarily by P450 2D6,[103–107] with frequent contributions from 1A2 and phase II metabolism.[23,79,103,107,108] 3A4 makes only a minor contribution to the metabolism of most phenothiazines.[106,109] Most of these agents display moderate to potent 2D6 inhibition.[110,111] As a class, they appear to be P-glycoprotein inhibitors, although several typical agents are P-glycoprotein substrates as well.[52,112,113]

Haloperidol Haloperidol's metabolism is quite complex, relying principally on P450 3A4 and phase II metabolism (not yet elucidated), with secondary contributions from 2D6 and 1A2.[114] It appears to be an in vitro P-glycoprotein substrate of weak affinity.[112,115] One of haloperidol's metabolites is a potent 2D6 inhibitor.[116] Haloperidol is also a P-glycoprotein inhibitor.[52,115]

Pimozide Pimozide is metabolized primarily by P450 3A4, with a secondary contribution by 1A2.[117] It is a potent inhibitor of 2D6 and moderate inhibitor of 3A4.[117] It is also an inhibitor of P-glycoprotein.[80] Because of its arrhythmogenic potential, this agent has a relatively low therapeutic index.

Atypical Antipsychotics

Aripiprazole Aripiprazole's metabolism is roughly equally divided between P450 2D6 and 3A4.[118] It lacks any known inhibitory or inductive capabilities. This agent, a par-

tial dopamine agonist, displays more avid binding to the dopamine D_2 receptor than any other antipsychotic.[119–122]

Clozapine Clozapine is principally metabolized by P450 1A2 with numerous secondary pathways, including 2C9/19, 2D6, 3A4, and UGT 1A3/4.[50,123–125] It appears to be an in vitro P-glycoprotein substrate of weak affinity.[112] It is also a known mild inhibitor of 2D6.[111,126] This agent has a fairly low therapeutic index.

Olanzapine Olanzapine is mostly metabolized by P450 1A2 and UGT 1A4, with 2D6 serving as a minor pathway.[23,127] It is also an in vitro P-glycoprotein substrate of low to moderate affinity[112] and a P-glycoprotein inhibitor.[52]

Quetiapine Quetiapine is mostly metabolized by P450 3A4.[128,129] It is also an in vitro P-glycoprotein substrate of moderate to strong affinity[112] and a P-glycoprotein inhibitor.[52]

Risperidone Most of risperidone's metabolism occurs through P45 2D6, although 3A4 also makes a significant contribution.[130–132] It is also an in vitro P-glycoprotein substrate of moderate to strong affinity.[112] Risperidone acts as a mild to moderate 2D6 inhibitor.[111,133]

Ziprasidone In healthy adults, ziprasidone is principally metabolized by aldehyde oxidase, with P450 3A4 serving as a secondary pathway.[26,134] It lacks any known inhibitory or inductive capabilities.

Mood Stabilizers

Carbamazepine Carbamazepine is primarily metabolized by P450 3A4, although 1A2, 2B6, 2C8/9, 2E1, and phase II metabolism (UGT 2B7) serve as minor pathways.[135–137] It is both a substrate and an inhibitor of P-glycoprotein, although its inhibitory capability is unlikely to be clinically significant.[138–140] It is also likely an inhibitor of 2C19, as evidenced by carbamazepine's ability to increase blood levels of both phenytoin and clomipramine.[141–143] Carbamazepine is a potent inducer of 3A4,[134,137,144,145] and it also induces 1A2, 2B6, 2C8/9, and UGT 1A4.[146–149]

Lamotrigine Lamotrigine is primarily metabolized by UGT 1A4,[22,23] although one or more P450 enzymes, not yet well characterized, serve as a secondary pathway. However, this P450 pathway leads to the generation of toxic metabolites.[150] In the presence of a UGT 1A4 inhibitor such as valproate, a greater proportion of lamotrigine is metabolized through this P450 metabolic pathway, leading to production of these toxic metabolites. This effect helps to explain why the combination of valproate and lamotrigine is associated with a greater incidence of both Stevens-Johnson syndrome and toxic epidermal necrolysis, even when low dosages of lamotrigine are used. Some weak autoinduction (at UGT 1A4) has been noted.[151]

Lithium Lithium is purely renally excreted, with no hepatic metabolic component. It lacks any inhibitory or inductive capabilities.

Oxcarbazepine Oxcarbazepine is quickly metabolized to an active monohydroxyoxcarbazepine (MHD) metabolite by the action of arylketone reductase. Both oxcarbazepine and MHD are metabolized in part through phase II glucuronidation.[152] Oxcarbazepine is a mild inducer of 3A4,[153] and a moderate inducer of UGT 1A4.[154] MHD is an inhibitor of 2C19.[141]

Phenytoin Phenytoin is primarily a substrate of P450 2C9 and 2C19,[141,155,156] with minor contributions from multiple UGT 1A family enzymes.[157] It is also a P-glycoprotein substrate.[158] It induces multiple enzymes, including 2B6, 2C9/19, 3A4, and UGTs 1A1 and 1A4.[147,149,159–162]

Topiramate Topiramate is primarily renally excreted. Its hepatic metabolism is mostly governed by phase II enzymes with a minor phase I contribution, neither of which has been well characterized.[163,164] It is likely to be a P-glycoprotein substrate.[165] It is an inhibitor of 2C19[166,167] and a mild inducer of 3A4.[168,169]

Valproate Valproate's metabolism is exceedingly complex, involving multiple phase I and II pathways (P450 2A6 and 2C9[170]; UGT 1A6, 1A9, and 2B7[171]) as well as β-oxidation.[172] It is a moderate inhibitor of 2C9.[173] It also inhibits multiple UGTs, including 1A4, 1A9, 2B7, and 2B15,[149,151,171] as well as epoxide hydrolase, the enzyme that metabolizes the principal metabolite of carbamazepine (carbamazepine-10,11-epoxide).[137,174,175] It is unclear if valproate has any meaningful inductive capabilities. Agents that induce the metabolism of valproate through 2C9 and 2A6 (such as phenytoin) lead to the increased production of the hepatotoxic 4-ene-valproate metabolite.[170]

DISCUSSION

Appendix 1 lists significant drug-drug interactions involving antidepressants and other psychotropic agents. In gen-

eral, these interactions involve substrate-inhibitor pairings, in which substrate blood levels are increased. For instance, the combination of fluoxetine and risperidone will lead to an average increase of 75% in the blood level of the risperidone active moiety (the combined concentrations of risperidone and its equipotent 9-hydroxy-risperidone metabolite).[176] Appendix 2 lists significant drug-drug interactions involving antipsychotics and other psychotropic agents. In these interactions, the antipsychotic agents generally play the role of substrates in substrate-inhibitor and/or substrate-inducer pairings. Appendix 3 lists significant drug-drug interactions involving mood stabilizers and other psychotropic agents. Because several of these agents are anticonvulsants, they are often involved as inducers of the metabolism of other agents. Lithium and valproate are notable exceptions to this generalization.

In all of these drug-drug interactions tables, only those interactions that are both reasonably frequent and problematic are included. For instance, the combination of lithium and haloperidol can produce an encephalopathic state,[28,177] and lithium plus fluoxetine can yield a central serotonin syndrome.[178,179] However, both of these combinations are common and well tolerated the vast majority of the time. In contrast, the combination of fluoxetine and quetiapine reliably produces increases in the peak and trough concentrations of quetiapine that are statistically significant but usually not clinically significant.[180] Hence, none of these drug-drug interactions are included in the tables.

Some ubiquitous nonpsychotropic agents/influences, such as tobacco (smoked) and oral contraceptives containing ethinylestradiol, create drug-drug interactions with numerous psychotropic agents. "Classic" drug-drug interactions include those between lithium and diuretics[28,181] and between acetylsalicylic acid and valproate.[182] By virtue of their special importance, selected examples of such interactions have been included in Appendix 4, along with some drug-drug interactions involving other psychotropic agents (anxiolytics, caffeine, etc.).

Although reviews such as this one may prove helpful to the clinician, they also make it clear that the broad range of information on drug-drug interactions severely tests the limits of human recall. It is simply not practical to insist that memorization of all the permutations of drug-drug interactions become the standard of care. However, recognition that the clinician cannot be expected to remember all of these details is small consolation to our patients, who will be harmed by drug-drug interactions. The only reasonable approach lies in the realm of computers. We urgently need programs that will supply information on drug-drug interactions in a manner that is both complete and efficient, but development of such tools presents considerable challenges. The more complete a drug-drug interactions database is, the more nonspecific the warnings become, and this characteristic increases obstructions to physicians' workflow. However, programs that ideally optimize completeness and efficiency might not become available for decades. In the interim, for the sake of our patients, we must somehow grapple with this imposing and evolving body of information. In that spirit, the following practical drug-drug interaction "survival tips" are offered for the busy clinician:

1) Become an "expert" on the drugs you prescribe most frequently. In absolute terms, the number of psychotropic agents is fairly modest, and most psychiatrists prescribe a limited group of 10 to 20 drugs far more often than they prescribe the remaining psychotropic agents. It is both reasonable and practical for clinicians to acquire a solid knowledge of the drug-drug interactions involving this specific subset of agents.

2) Pay special attention to agents that have a low therapeutic index (the lethal dose for 50% of the population divided by the effective dose for 50% of the population [LD_{50}/ED_{50}]). Most of the more recently developed and released psychotropics are safer in overdose than their predecessors. Thus, a drug-drug interaction that produces a significant increase in the blood level of, for instance, mirtazapine, is unlikely to yield a truly dangerous outcome.[90] However, agents such as TCAs and lithium are potentially lethal in overdose.[183,184] Accordingly, drug-drug interactions that produce significant increases in the blood levels of these agents can lead to severe morbidity and mortality. Acquiring a detailed understanding of the drug-drug interactions involving these agents will largely prevent such adverse events.

3) Consult resources frequently. Gather reliable references (articles, books, tables, computer programs, etc.) and refer to them whenever a drug-drug interaction is suspected. This vigilance serves two functions. First, it encourages a mindset in which one does not rely solely on personal powers of recall to make clinical decisions. Although such reliance is consistent with typical modes of practice and the standard of care, it is manifestly dangerous to our patients. A physician who makes frequent use of auxiliary resources is a safer clinician. Second, repeated use of these resources when dealing with actual patients in real situations is the best way to become familiar with clinically relevant drug-drug interactions.

4) Educate your patients to be their own last, best line

of defense in the prevention of drug-drug interactions. Patients should be encouraged to keep a current list of all medications, over-the-counter remedies, herbal products, and pertinent dietary and lifestyle concerns (smoking, consumption of grapefruit juice or green tea, etc.), and they should present this list to all health care providers and to their pharmacist(s). In addition, they should be encouraged to have all of their prescriptions filled at the same pharmacy and specifically to enroll in that pharmacy's drug interaction monitoring program. This precaution will greatly reduce—although not eliminate[185]—the likelihood of a drug-drug interaction.

5) Try to select agents that minimize the risk of precipitating a drug-drug interaction. For instance, among the macrolide antibiotics, azithromycin provides similar efficacy to erythromycin and clarithromycin. However, the latter two agents are potent inhibitors of both P450 3A4 and P-glycoprotein.[186,187] Azithromycin is not a significant inhibitor of either 3A4 or P-glycoprotein,[188] hence it is significantly less likely than its cousins to produce drug-drug interactions. Similar arguments can be made for the antidepressants venlafaxine and mirtazapine, which are not clinically significant P450 inhibitors,[90,189] and for pravastatin and rosuvastatin, hydroxymethylglutaryl–coenzyme A reductase inhibitors that are not P450 3A4 substrates and are less likely than other agents in the class to produce toxicity because of impaired metabolism.[190,191]

CONCLUSION

The understanding of intrapsychotropic drug-drug interactions has improved dramatically in recent years. However, the amount of information can seem overwhelming, leading the clinician to either ignore the topic or withdraw into a therapeutic paralysis. In the future, it is likely that sophisticated computer programs will allow clinicians to prescribe in an efficient yet truly safe manner. Until that day arrives, we hope that this review and these recommendations will prove useful in helping psychiatrists to anticipate and avoid drug-drug interactions.

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APPENDIX 1. Significant Drug-Drug Interactions Involving Antidepressants

Antidepressant and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Bupropion				
Carbamazepine	Decreased level of bupropion[192, 193]	Induction of P450 2B6 by carbamazepine[83, 147]	Possible loss of therapeutic efficacy	
Duloxetine	Increased level of duloxetine	Inhibition of P450 2D6 by bupropion[84, 86, 87]	Dry mouth, constipation, fatigue, sedation, increased sweating	Theoretical concern
Fluoxetine	Increased level of bupropion[85]	Inhibition of P450 2B6 by fluoxetine plus norfluoxetine[42, 83]	Increased risk of seizures	Theoretical concern
Fluvoxamine	Increased level of bupropion[85]	Inhibition of P450 2B6 by fluvoxamine[42, 83]	Increased risk of seizures	Theoretical concern
Monoamine oxidase inhibitors (MAOIs)	n/a	Decreased metabolism of norepinephrine by MAOIs, combined with norepinephrine reuptake inhibition by bupropion	Increased risk of hypertensive crisis[18, 19, 85]	Potentially fatal
Nefazodone	Increased level of metachlorophenyl-piperazine (mCPP)	Inhibition of P450 2D6 by bupropion[84, 98]	Acute dysphoric anxiety	Theoretical concern
Paroxetine	Increased level of bupropion[85]	Inhibition of P450 2B6 by paroxetine[42, 83]	Increased risk of seizures	Theoretical concern
Phenothiazine antipsychotics	Increased levels of phenothiazine antipsychotics[85, 194]	Inhibition of P450 2D6 by bupropion[84, 103, 104, 107]	Increased extrapyramidal side effects (EPS) and other side effects	Combination of bupropion with mesoridazine or thioridazine can increase arrhythmogenic potential
Phenytoin	Decreased level of bupropion	Induction of P450 2B6 by phenytoin[83, 147]	Possible loss of therapeutic efficacy	Theoretical concern, but likely
Sertraline	Increased level of bupropion[85]	Inhibition of P450 2B6 by sertraline[42, 83]	Increased risk of seizures	Theoretical concern
Tricyclic anti-depressants (TCAs)	Increased levels of TCAs[84, 85]	Inhibition of P450 2D6 by bupropion[21, 64, 65, 75, 84, 195]	Increased arrhythmia risk and anticholinergic symptoms	
Citalopram, escitalopram				
Carbamazepine	Decreased levels of citalopram and of escitalopram[196]	Induction of P450 3A4 by carbamazepine[32, 33, 37, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
MAOIs	n/a	Decreased metabolism of serotonin by MAOIs, combined with serotonin reuptake inhibition by citalopram and by escitalopram	Central serotonin syndrome[18, 19, 35, 38]	Potentially fatal
Phenothiazine antipsychotics	Increased levels of phenothiazine antipsychotics	Inhibition of P450 2D6 by citalopram and by escitalopram[31, 34, 103, 104, 107]	Increased EPS and other side effects	Combination of citalopram or escitalopram with mesoridazine or thioridazine can increase arrhythmogenic potential (theoretical concern)
Phenytoin	Decreased levels of citalopram and escitalopram	Induction of P450 3A4 and 2C19 by phenytoin[32, 33, 159–161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Pimozide	n/a	Unclear pharmacodynamic effect	Increase in the QT interval without an increase in the level of pimozide[35, 38]	Theoretical concern
Secondary amine TCAs	Increased levels of secondary amine TCAs[35, 38]	Inhibition of P450 2D6 by citalopram and by escitalopram[21, 31, 34, 64, 195]	Increased arrhythmia risk and anticholinergic symptoms	
Duloxetine				
Bupropion	Increased level of duloxetine	Inhibition of P450 2D6 by bupropion[84, 86, 87]	Dry mouth, constipation, fatigue, sedation, increased sweating	Theoretical concern
Carbamazepine	Decreased level of duloxetine	Induction of P450 1A2 by carbamazepine[37, 146]	Possible loss of therapeutic efficacy	Theoretical concern
Fluoxetine, paroxetine	Increased level of duloxetine[87]	Inhibition of P450 2D6 by fluoxetine plus norfluoxetine or by paroxetine[34, 40, 54, 86]	Dry mouth, constipation, fatigue, sedation, increased sweating	
Fluvoxamine	Increased level of duloxetine[87]	Inhibition of P450 1A2>>2D6 by fluvoxamine[34, 37, 48, 86]	Dry mouth, constipation, fatigue, sedation, increased sweating	
MAOIs	n/a	Decreased metabolism of serotonin and norepinephrine by MAOIs, combined with serotonin and norepinephrine reuptake inhibition by duloxetine	Central serotonin syndrome and/or hypertensive crisis[18, 19, 87]	Potentially fatal

APPENDIX 1. Significant Drug-Drug Interactions Involving Antidepressants (*continued*)

Antidepressant and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Paroxetine	Increased level of duloxetine	See information for interaction of duloxetine and fluoxetine, paroxetine	See information for interaction of duloxetine and fluoxetine, paroxetine	
Phenothiazine antipsychotics	Increased levels of phenothiazine antipsychotics[87]	Inhibition of P450 2D6 by duloxetine[86, 103, 104, 107]	Increased EPS and other side effects	Combination of duloxetine with mesoridazine or thioridazine can increase arrhythmogenic potential
TCAs	Increased levels of TCAs[87]	Inhibition of P450 2D6 by duloxetine[21, 64, 65, 75, 86, 195]	Increased arrhythmia risk and anticholinergic symptoms	
Fluoxetine				
Bupropion	Increased level of bupropion[85]	Inhibition of P450 2B6 by fluoxetine plus norfluoxetine[42, 83]	Increased risk of seizures	Theoretical concern
Carbamazepine	Increased level of carbamazepine[199]	Inhibition of multiple P450 enzymes (3A4, 1A2, 2B6, 2C9)[41–43, 46, 60, 135, 200] and P-glycoprotein[47, 138] by fluoxetine plus norfluoxetine	Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.	
Clozapine	Increased level of clozapine[201]	Inhibition of P450 1A2, 2C9/19, 2D6, and 3A4,[34, 40, 41, 43, 44, 46, 60, 123, 124] as well as P-glycoprotein[47, 112] (weak contribution) by fluoxetine plus norfluoxetine	Increased sedation, anticholinergic symptoms, seizure risk, etc.	Clozapine levels typically increase by roughly 50% with this combination
Duloxetine	Increased level of duloxetine[87]	Inhibition of P450 2D6 by fluoxetine plus norfluoxetine[34, 40, 86]	Dry mouth, constipation, fatigue, sedation, increased sweating	
MAOIs	n/a	Decreased metabolism of serotonin by MAOIs, combined with serotonin reuptake inhibition by fluoxetine plus norfluoxetine	Central serotonin syndrome[178, 202]	Potentially fatal
Nefazodone	Increased level of mCPP[203]	Inhibition of P450 2D6 by fluoxetine plus norfluoxetine[34, 40, 97, 98]	Acute dysphoric anxiety	
Phenytoin	Increased level of phenytoin[204]	Inhibition of both P450 2C9/19[43,44,68,155,156] and P-glycoprotein[47, 158] by fluoxetine plus norfluoxetine	Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.	
Pimozide	Increased level of pimozide (probably)	Inhibition of P450 1A2 and 3A4 by fluoxetine plus norfluoxetine (probably)[41, 46, 60]	Increased EPS and arrhythmogenic potential	One known case of serious bradycardia[205]
Risperidone	Increased level of risperidone[176]	Inhibition of P450 2D6/3A4[34, 40, 46, 60, 130] and P-glycoprotein[47, 112] by fluoxetine plus norfluoxetine	EPS, increased prolactin	Average increase in the ‘‘risperidone active moiety’’ (sum of risperidone and 9 hydroxy risperidone) of roughly 75%
TCAs	Increased levels of TCAs[20, 75, 206, 207]	Inhibition of multiple P450 enzymes[21, 34, 40, 41, 43, 44, 46, 60, 64, 75–77] and P-glycoprotein[36, 47, 69, 70, 208] by fluoxetine plus norfluoxetine	Increased arrhythmia risk and anticholinergic symptoms	
Typical antipsychotics	Increased levels of most typical antipsychotics[194, 209]	Inhibition of multiple P450 enzymes (1A2, 2D6, and 3A4)[34,40,41,46,60,103–105,107,210] and P-glycoprotein[47, 52, 112] by fluoxetine plus norfluoxetine	Increased EPS and other side effects	Combination of fluoxetine with mesoridazine, thioridazine, or pimozide can increase arrhythmogenic potential
Fluvoxamine				
Bupropion	Increased level of bupropion[85]	Inhibition of P450 2B6 by fluvoxamine[42, 83]	Increased risk of seizures	Theoretical concern
Carbamazepine	1) Increased level of carbamazepine[211, 212] and 2) decreased level of fluvoxamine	1) Inhibition of multiple P450 enzymes (3A4, 1A2, 2B6, 2C9)[42, 43, 45, 48, 50, 51, 135, 200] and P-glycoprotein[47, 52, 138] by fluvoxamine; 2) induction of P450 1A2 by carbamazepine[48, 146]	Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.	Decrease in fluvoxamine levels is a theoretical concern
Clozapine	Increased level of clozapine[213–216]	Inhibition of P450 1A2, 2C9/19, 2D6 (weak) and 3A4,[34, 45, 48, 50, 51, 123, 124] as well as P-glycoprotein (weak contribution)[47, 52, 112] by fluvoxamine	Increased sedation, anticholinergic symptoms, seizure risk, etc.	Clozapine levels can increase three- to fourfold

Duloxetine	Increased level of duloxetine[87]	Inhibition of P450 1A2>>2D6 by fluvoxamine[34, 37, 48, 86]	Dry mouth, constipation, fatigue, sedation, increased sweating	
MAOIs	n/a	Decreased metabolism of serotonin by MAOIs, combined with serotonin reuptake inhibition by fluvoxamine	Central serotonin syndrome[18, 19, 217]	Potentially fatal
Mirtazapine	Increased level of mirtazapine[218]	Inhibition of P450 1A2, 2D6, and 3A4 by fluvoxamine[34, 48, 50, 88, 89]	Somnolence (perhaps), increased risk of serotonin syndrome[219]	This combination can increase mirtazapine levels by as much as fourfold
Olanzapine	Increased level of olanzapine[127, 220]	Inhibition of P450 1A2 (strong), 2D6 (weak), and P-glycoprotein by fluvoxamine[34, 47, 48, 52, 112, 127]	Increased sedation and risk of EPS	
Pimozide	Increased level of pimozide (probably)[217]	Inhibition of P450 1A2 and 3A4 by fluvoxamine[45, 48, 50, 117]	Increased EPS and arrhythmogenic potential	Theoretical concern
Phenytoin	Increased level of phenytoin[221, 222]	Inhibition of both P450 2C9/19 and P-glycoprotein by fluvoxamine[45, 47, 48, 51, 52, 155, 156, 158]	Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.	
Tertiary amine TCAs	Increased levels of tertiary amine TCAs[75, 223, 224]	Inhibition of multiple P450 enzymes and P-glycoprotein by fluvoxamine[34, 36, 45, 47, 48, 50, 52, 63, 65, 73–77, 208]	Increased arrhythmia risk and anticholinergic symptoms	
Typical antipsychotics	Increased levels of most typical antipsychotics[194, 210, 225]	Inhibition of multiple P450 enzymes (1A2, 2D6, and 3A4) and P-glycoprotein by fluvoxamine[34,47,48,50,52,103–105,107,112,210]	Increased EPS and other side effects	Combination of fluvoxamine with mesoridazine, thioridazine, or pimozide can increase arrhythmogenic potential
MAOIs				
All other anti-depressants (except for low-dose trazodone)[226]	n/a	Decreased metabolism of serotonin and norepinephrine (and sometimes dopamine) by MAOIs, combined with serotonin, norepineprine, and dopamine reuptake inhibition by other antidepressants	Central serotonin syndrome and/or hypertensive crisis[18, 19, 202, 227]	Potentially fatal
Clozapine	n/a	Decreased metabolism of norepinephrine by MAOIs, combined with increased serum norepinephrine due to clozapine's α_2 blockade[181, 228]	Hypertension	One case known to the authors
Stimulants	n/a	Decreased metabolism of norepinephrine and dopamine by MAOIs, combined with norepinephrine and dopamine reuptake inhibition by stimulants	Hypertensive crisis[18, 19]	Potentially fatal
Ziprasidone	n/a	Decreased metabolism of serotonin and norepinephrine by MAOIs, combined with ziprasidone's intrinsic serotonergic and noradrenergic reuptake blockade	Central serotonin syndrome and/or hypertensive crisis[229]	Potentially fatal, but a theoretical concern for this combination
Mirtazapine				
Carbamazepine	Decreased level of mirtazapine[230]	Induction of P450 1A2 and 3A4 by carbamazepine[88, 89, 134, 137, 145, 146, 197, 198]	Possible loss of therapeutic efficacy	
Fluvoxamine	Increased level of mirtazapine[218]	Inhibition of P450 1A2, 2D6, and 3A4 by fluvoxamine[34, 48, 50, 88, 89]	Somnolence (perhaps), increased risk of serotonin syndrome[219]	This combination can increase mirtazapine levels by as much as fourfold
MAOIs	n/a	Decreased metabolism of serotonin and norepinephrine by MAOIs, combined with increased presynaptic release of serotonin and norepinephrine by mirtazapine	Central serotonin syndrome and/or hypertensive crisis[18, 19, 90]	Potentially fatal
Phenytoin	Decreased level of mirtazapine[231]	Induction of P450 3A4 by phenytoin[88, 89, 160, 161, 198]	Possible loss of therapeutic efficacy	
Nefazodone				
Bupropion	Increased levels of mCPP	Inhibition of P450 2D6 by bupropion[84, 98]	Acute dysphoric anxiety	Theoretical concern
Carbamazepine	1) Increased level of carbamazepine and 2) decreased level of nefazodone[232]	1) Inhibition of P450 3A4 by nefazodone[46, 100, 135, 200]; 2) induction of P450 3A4 by carbamazepine[97, 134, 137, 145, 197, 198]	1) Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.; 2) likely loss of therapeutic efficacy	

APPENDIX 1. Significant Drug-Drug Interactions Involving Antidepressants (*continued*)

Antidepressant and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Fluoxetine	Increased levels of mCPP[203]	Inhibition of P450 2D6 by fluoxetine plus norfluoxetine[34, 40, 97, 98]	Acute dysphoric anxiety	
MAOIs	n/a	Decreased metabolism of serotonin and norepinephrine by MAOIs, combined with serotonin and norepinephrine reuptake inhibition by nefazodone	Central serotonin syndrome and/or hypertensive crisis[18, 19, 95]	Potentially fatal
Paroxetine	Increased levels of mCPP	Inhibition of P450 2D6 by paroxetine[34, 67, 97, 98]	Acute dysphoric anxiety	Theoretical concern
Phenytoin	Decreased level of nefazodone	Induction of P450 3A4 by phenytoin[97, 161, 198]	Likely loss of therapeutic efficacy	Theoretical concern, but likely
Pimozide	Increased levels of 1) pimozide[186, 233] and 2) mCPP	Inhibition of 1) P450 3A4 by nefazodone[46, 100, 117] and 2) P450 2D6 by pimozide[97, 98, 117]	1) Increased risk of QT prolongation leading to a malignant arrhythmia and 2) acute dysphoric anxiety	1) Potentially fatal and 2) theoretical concern
Paroxetine				
Bupropion	Increased level of bupropion[85]	Inhibition of P450 2B6 by paroxetine[42, 83]	Increased risk of seizures	Theoretical concern
Duloxetine	Increased level of duloxetine[87]	Inhibition of P450 2D6 by paroxetine[34, 54, 86]	Dry mouth, constipation, fatigue, sedation, increased sweating	
MAOIs	n/a	Decreased metabolism of serotonin by MAOIs, combined with serotonin reuptake inhibition by paroxetine	Central serotonin syndrome[18, 19, 53]	Potentially fatal
Nefazodone	Increased levels of mCPP	Inhibition of P450 2D6 by paroxetine[34, 67, 97, 98]	Acute dysphoric anxiety	Theoretical concern
Phenothiazine antipsychotics	Increased levels of phenothiazine antipsychotics[55, 194]	Inhibition of P450 2D6[34, 67, 103, 104, 107] and P-glycoprotein[47, 52, 112] by paroxetine	Increased EPS and other side effects	Combination of paroxetine with mesoridazine or thioridazine can increase arrhythmogenic potential
Risperidone	Increased level of risperidone[234]	Inhibition of P450 2D6>3A4 and P-glycoprotein by paroxetine[34, 47, 67, 112, 130]	EPS, increased prolactin	Average increase in the ''risperidone active moiety'' (sum of risperidone and 9-hydroxy risperidone) of roughly 45%
TCAs	Increased levels of TCAs[54, 75, 206, 235, 236]	Inhibition of P450 2D6 and P-glycoprotein by paroxetine[21, 34, 36, 47, 64, 65, 67, 69, 70, 75, 195, 208]	Increased arrhythmia risk and anticholinergic symptoms	
Sertraline				
Bupropion	Increased level of bupropion[85]	Inhibition of P450 2B6 by sertraline[42, 83]	Increased risk of seizures	Theoretical concern
Carbamazepine	Decreased level of sertraline[237]	Induction of P450 2B6, 2C9, and 3A4 by carbamazepine[43, 56, 57, 134, 137, 145, 147, 148, 197, 198]	Possible loss of therapeutic efficacy	
Lamotrigine	Increased level of lamotrigine[62]	Inhibition of uridine 5′-diphosphate glucuronosyltransferase (UGT) 1A4 by sertraline[22, 23, 62]	Increased somnolence, confusion; increased risk of emergence of rash	Lamotrigine levels typically double with this combination. Risk of rash and risk of progression to Stevens-Johnson syndrome or toxic epidermal necrolysis exist with this combination.[150, 151]
MAOIs	n/a	Decreased metabolism of serotonin by MAOIs, combined with serotonin reuptake inhibition by sertraline	Central serotonin syndrome[18, 19, 227, 238]	Potentially fatal
Phenytoin	Decreased level of sertraline[237]	Induction of P450 2B6, 2C9/19, and 3A4 by phenytoin[56, 57, 147, 159, 161, 198]	Possible loss of therapeutic efficacy	
Pimozide	Unclear; possible increased level of pimozide[233]	Unclear; possible inhibition of P450 3A4 and 1A2 by sertraline[41, 59–61, 239]	Increased EPS and arrhythmogenic potential	
TCAs	Increased levels of TCAs[58, 236, 240]	Inhibition of multiple P450 enzymes (mostly 2D6 and 2C19)[21, 34, 41, 44, 58–61, 64, 75–77, 195] and P-glycoprotein[36, 47, 69, 70, 208] by sertraline	Increased arrhythmia risk and anticholinergic symptoms	

TCAs				
Bupropion	Increased levels of TCAs[84, 85]	Inhibition of P450 2D6 by bupropion[21, 64, 65, 75, 84, 195]	Increased arrhythmia risk and anticholinergic symptoms	
Carbamazepine	1) Decreased levels of TCAs[195, 241], 2) except for level of clomipramine, which is reportedly increased[142]	1) Induction of P450 1A2, 2C9, and 3A4 and UGT 1A4 by carbamazepine[43, 74–76, 78, 134, 137, 145, 146, 148, 149, 197, 198]; 2) inhibition of P450 2C19 by carbamazepine[75, 141]	Possible loss of therapeutic efficacy	It is confusing that amitriptyline, which also relies strongly on P450 2C19 for its metabolism, should be reliably decreased by carbamazepine[195], while clomipramine is reportedly increased. Carbamazepine's activity at P450 2C8/9 and 2C19 is not yet completely understood
Citalopram, escitalopram	Increased levels of secondary amine TCAs[35, 38]	Inhibition of P450 2D6 by citalopram and by escitalopram[21, 31, 34, 64, 195]	Increased arrhythmia risk and anticholinergic symptoms	
Duloxetine	Increased levels of TCAs[87]	Inhibition of P450 2D6 by duloxetine[21, 64, 65, 75, 86, 195]	Increased arrhythmia risk and anticholinergic symptoms	
Fluoxetine	Increased levels of TCAs[20, 75, 206, 207]	Inhibition of both multiple P450 enzymes[21, 34, 40, 41, 43, 44, 46, 60, 64, 75–77, 195] and P-glycoprotein[36, 47, 69, 70, 208] by fluoxetine plus norfluoxetine	Increased arrhythmia risk and anticholinergic symptoms	
Fluvoxamine	Increased levels of tertiary amine TCAs[75, 223, 224]	Inhibition of both multiple P450 enzymes and P-glycoprotein by fluvoxamine[34, 36, 45, 47, 48, 50, 52, 63, 65, 73–77, 208]	Increased arrhythmia risk and anticholinergic symptoms	
Haloperidol	Increased levels of TCAs	Inhibition of P450 2D6 and P-glycoprotein by haloperidol and reduced haloperidol metabolites[21,36,52,64,69,70,111,115,116,195,208]	Increased arrhythmia risk and anticholinergic symptoms	Theoretical concern
MAOIs	n/a	Decreased metabolism of serotonin and norepinephrine by MAOIs, combined with serotonin and norepinephrine reuptake inhibition by TCAs	Central serotonin syndrome and/or hypertensive crisis[18, 19, 183]	Potentially fatal
Paroxetine	Increased levels of TCAs[54, 75, 206, 235, 236]	Inhibition of P450 2D6 and P-glycoprotein by paroxetine[21,34,36,47,64,65,67,69,70,75,195,208]	Increased arrhythmia risk and anticholinergic symptoms	
Phenothiazine antipsychotics	Increased levels of TCAs[73, 110, 195, 242]	Inhibition of P450 2D6 and P-glycoprotein by phenothiazine antipsychotics[21, 36, 52, 64, 69, 70, 110, 111, 113, 195, 208] (also yielding increased arrhythmogenic potential through pharmacodynamic synergy with mesoridazine and thioridazine)	Increased arrhythmia risk and anticholinergic symptoms	Combination of TCAs with mesoridazine or thioridazine can increase arrhythmogenic potential
Phenytoin	Decreased levels of TCAs	Induction of P450 2C19 and 3A4 and UGT 1A4 by phenytoin[74–76, 78, 149, 159–161, 198]	Possible loss of therapeutic efficacy	Theoretical, but likely
Pimozide	Increased levels of TCAs	Inhibition of P450 2D6, 3A4, and P-glycoprotein by pimozide[21, 36, 64, 69, 70, 74–76, 80, 117, 195, 208], in addition to synergistic QT prolongation[233]	Increased arrhythmogenic potential	Theoretical concern
Sertraline	Increased levels of TCAs[58, 236, 240]	Inhibition of both multiple P450 enzymes (mostly 2D6 and 2C19)[21, 34, 41, 44, 58–61, 64, 75–77, 195] and P-glycoprotein[36, 47, 69, 70, 208] by sertraline	Increased arrhythmia risk and anticholinergic symptoms	
Ziprasidone	n/a	Synergistic QT prolongation[26, 243]	Increased arrhythmogenic potential	
Venlafaxine				
MAOIs	n/a	Decreased metabolism of serotonin, norepinephrine, and sometimes dopamine by MAOIs, combined with serotonin, norepinephrine, and dopamine reuptake inhibition by venlafaxine	Central serotonin syndrome and/or hypertensive crisis[18, 19, 189]	Potentially fatal

APPENDIX 2. Significant Drug-Drug Interactions Involving Antipsychotics

Antipsychotic and Interacting Drugs	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Aripiprazole				
All other antipsychotic agents	Significant displacement of other antipsychotics from the dopamine D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of aripiprazole[118]	Induction of P450 3A4 by carbamazepine[118, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
Phenytoin	Decreased level of aripiprazole	Induction of P450 3A4 by phenytoin[118, 160, 161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Clozapine				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of clozapine[214, 244, 245]	Induction of P450 1A2, 2C9, 3A4, and uridine 5′-diphosphate glucuronosyltransferase (UGT) 1A4 by carbamazepine[43, 50, 123–125, 134, 137, 145, 146, 148, 149, 197, 198]	Possible loss of therapeutic efficacy	Synergistic risk of blood dyscrasias (agranulocytosis from clozapine and aplastic anemia from carbamazepine)[246]
Fluoxetine	Increased level of clozapine[201]	Inhibition of P450 1A2, 2C9/19, 2D6, and 3A4[34, 40, 41, 43, 44, 46, 60, 123, 124], as well as P-glycoprotein[47, 112] (weak contribution to clozapine bioavailability) by fluoxetine plus norfluoxetine	Increased sedation, anticholinergic symptoms, seizure risk, etc.	Clozapine levels typically increase by roughly 50% with this combination
Fluvoxamine	Increased level of clozapine[213–216]	Inhibition of P450 1A2, 2C9/19, 2D6 (weak) and 3A4[34, 45, 48, 50, 51, 123, 124], as well as P-glycoprotein (weak contribution)[47, 52, 112] by fluvoxamine	Increased sedation, anticholinergic symptoms, seizure risk, etc.	Clozapine levels can increase three- to fourfold
Monoamine oxidase inhibitors (MAOIs)	n/a	Decreased metabolism of norepinephrine by MAOIs, combined with increased serum norepinephrine due to clozapine's α_2 blockade	Hypertension	One case known to the authors
Phenytoin	Decreased level of clozapine[247]	Induction of P450 2C9/19, 3A4 and UGT 1A4 by phenytoin[50, 123–125, 149, 159–161, 198]	Possible loss of therapeutic efficacy	
Haloperidol				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of haloperidol[244, 248, 249]	Induction of P450 1A2 and 3A4 (and possibly pertinent phase II enzymes) by carbamazepine[114,134,137,145,146,149,197,198]	Possible loss of therapeutic efficacy	
Fluvoxamine	Increased level of haloperidol[210, 250]	Inhibition of P450 1A2, 3A4, and P-glycoprotein by fluvoxamine[45, 47, 48, 50, 52, 112, 114, 115]	Increased EPS and other side effects	

Phenytoin	Decreased level of haloperidol[251]	Induction of P450 3A4 (and possibly pertinent phase II enzymes) by phenytoin[149, 160–162, 198]	Possible loss of therapeutic efficacy	
Tricyclic antidepressants (TCAs)	Increased levels of TCAs	Inhibition of P450 2D6 and P-glycoprotein by haloperidol and reduced haloperidol metabolites[21,36,52,64,69,70,111,115,116,195,208]	Increased arrhythmia risk and anticholinergic symptoms	Theoretical concern
Olanzapine				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of olanzapine[252, 253]	Induction of P450 1A2 and UGT 1A4 by carbamazepine[22, 23, 127, 146, 149]	Possible loss of therapeutic efficacy	
Fluvoxamine	Increased level of olanzapine[127, 220]	Inhibition of P450 1A2 (strong), 2D6 (weak), and P-glycoprotein by fluvoxamine[34, 47, 48, 52, 112, 127]	Increased sedation and risk of extrapyramidal symptoms (EPS	
Phenytoin	Decreased level of olanzapine	Induction of UGT 1A4 by phenytoin[22, 23, 149]	Possible loss of therapeutic efficacy	Theoretical concern, but likely
Pimozide				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of pimozide	Induction of P450 1A2 and 3A4 by carbamazepine[117, 134, 137, 145, 146, 197, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Citalopram, escitalopram	n/a	Unclear pharmacodynamic effect	Increase in the QT interval without an increase in the level of pimozide[35, 38]	Theoretical concern
Fluoxetine	Increased level of pimozide (probably	Inhibition of P450 1A2 and 3A4 by fluoxetine plus norfluoxetine (probably)[41, 46, 60]	Increased EPS and arrhythmogenic potential	One known case of serious bradycardia[205]
Fluvoxamine	Increased level of pimozide (probably)	Inhibition of P450 1A2 and 3A4 by fluvoxamine[45, 48, 50, 117]	Increased EPS and arrhythmogenic potential	Theoretical concern
Nefazodone	Increased levels of 1) pimozide[186, 233] and 2) metachlorophenylpiperazine	Inhibition of 1) P450 3A4 by nefazodone[46, 100, 117]; 2) P450 2D6 by pimozide[97, 98, 117]	1) Increased risk of QT prolongation leading to a malignant arrhythmia; 2) acute dysphoric anxiety	1) Potentially fatal; 2) theoretical concern
Phenytoin	Decreased level of pimozide	Induction of P450 3A4 by phenytoin[117, 160, 161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Sertraline	Unclear; possible increased level of pimozide[233]	Unclear; possible inhibition of P450 3A4 and 1A2 by sertraline[41, 59–61, 239]	Increased EPS and arrhythmogenic potential	
TCAs	Increased levels of TCAs	Inhibition of P450 2D6, 3A4 and P-glycoprotein by pimozide[21, 36, 64, 69, 70, 74–76, 80, 117, 195, 208], in addition to synergistic QT prolongation[233]	Increased arrhythmogenic potential	Theoretical concern
Ziprasidone	n/a	Synergistic QT prolongation[26]	Increased arrhythmogenic potential	Theoretical concern
Quetiapine				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	

APPENDIX 2. Significant Drug-Drug Interactions Involving Antipsychotics (*continued*)

Antipsychotic and Interacting Drugs	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Carbamazepine	1) Decreased level of quetiapine[129, 254] and 2) increased level of carbamazepine-10,11-epoxide[255]	1) Induction of P450 3A4 by carbamazepine[128, 129, 134, 137, 145, 197, 198]; 2) mechanism unknown, but possibly inhibition of epoxide hydrolase	1) Possible (or even likely) loss of therapeutic efficacy; 2) possible ataxia, nausea, sedation, confusion, dysarthria, diplopia, tremor, etc	
Phenytoin	Decreased level of quetiapine[256]	Induction of P450 3A4 by phenytoin[128, 129, 160, 161, 198]	Likely loss of therapeutic efficacy	Fivefold increase in the clearance of quetiapine with this combination
Risperidone				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of risperidone[257–259]	Induction of P450 3A4 by carbamazepine[130, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
Fluoxetine, paroxetine	Increased level of risperidone[176, 234]	Inhibition of P450 2D6>3A4[34, 40, 46, 60, 67, 130] and P-glycoprotein[47, 112] by fluoxetine plus norfluoxetine/paroxetine	EPS, increased prolactin	Average increase in the ''risperidone active moiety'' (sum of risperidone and 9-hydroxy risperidone) of roughly 75% when combined with fluoxetine and of roughly 45% when combined with paroxetine
Phenytoin	Decreased level of risperidone[130]	Induction of P450 3A4 by phenytoin[130, 160, 161, 198]	Possible loss of therapeutic efficacy	
Typical antipsychotics (general)				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Bupropion, citalopram, duloxetine, escitalopram, paroxetine	Increased levels of phenothiazine antipsychotics[85, 87, 194]	Inhibition of P450 2D6 by bupropion, paroxetine > citalopram, duloxetine, escitalopram[31, 34, 55, 67, 84, 86, 103, 104, 107] and P-glycoprotein[47, 52, 112] by paroxetine	Increased EPS and other side effects	Combination of mesoridazine or thioridazine with these agents can increase arrhythmogenic potential (of more theoretical concern with citalopram, duloxetine, escitalopram)
Carbamazepine	Decreased levels of typical antipsychotics[244]	Induction of P450 1A2, 3A4, and UGT 1A4 by carbamazepine[23, 79, 103, 107, 108, 114, 117, 134, 137, 145, 146, 149, 197, 198, 210]	Possible loss of therapeutic efficacy	
Citalopram, escitalopram	Increased levels of phenothiazine antipsychotics[85, 87, 194]	See information for interaction of typical antipsychotics with bupropion, citalopram, duloxetine, escitalopram, paroxetine	Increased EPS and other side effects	See information for interaction of typical antipsychotics with bupropion, citalopram, duloxetine, escitalopram, paroxetine
Duloxetine	Increased levels of phenothiazine antipsychotics[85, 87, 194]	See information for interaction of typical antipsychotics with bupropion, citalopram, duloxetine, escitalopram, paroxetine	Increased EPS and other side effects	See information for interaction of typical antipsychotics with bupropion, citalopram, duloxetine, escitalopram, paroxetine
Fluoxetine	Increased levels of most typical antipsychotics[194, 209]	Inhibition of multiple P450 enzymes (1A2, 2D6, and 3A4)[34, 40, 41, 46, 60, 103–105, 107, 210] and P-glycoprotein[47, 52, 112] by fluoxetine plus norfluoxetine	Increased EPS and other side effects	Combination of mesoridazine or thioridazine with fluoxetine can increase arrhythmogenic potential

Fluvoxamine	Increased levels of most typical antipsychotics[194, 210, 225]	Inhibition of multiple P450 enzymes (1A2, 2D6, and 3A4) and P-glycoprotein by fluvoxamine[34,47,48,50,52,103–105,107,112,210]	Increased EPS and other side effects	Combination of mesoridazine, thioridazine, or pimozide with fluvoxamine can increase arrhythmogenic potential
Paroxetine	Increased levels of phenothiazine antipsychotics[85, 87, 194]	See information for interaction of typical antipsychotics with bupropion, citalopram, duloxetine, escitalopram, paroxetine	Increased EPS and other side effects	See information for interaction of typical antipsychotics with bupropion, citalopram, duloxetine, escitalopram, paroxetine
Phenytoin	Decreased levels of typical antipsychotics[251]	Induction of P450 3A4 and UGT 1A4 by phenytoin[79, 106, 109, 149, 160, 161, 198]	Possible loss of therapeutic efficacy	
TCAs	Increased levels of TCAs[73, 110, 195, 242]	Inhibition of P450 2D6 and P-glycoprotein by phenothiazine antipsychotics[21, 36, 52, 64, 69, 70, 110, 111, 113, 195, 208] (also yielding increased arrhythmogenic potential through pharmacodynamic synergy in combination of TCAs with mesoridazine or thioridazine	Increased arrhythmia risk and anticholinergic symptoms	Combination of mesoridazine or thioridazine with TCAs can increase arrhythmogenic potential
Ziprasidone	n/a	Synergistic QT prolongation with chlorpromazine, mesoridazine, pimozide, or thioridazine[26]	Increased arrhythmogenic potential	Theoretical concern
Ziprasidone				
Aripiprazole	Significant displacement of other antipsychotics from the D_2 receptor during antipsychotic crossover titrations involving aripiprazole	Aripiprazole binds more avidly to the D_2 receptor than any other antipsychotic[118, 120–122]	Possible clinical decompensation during antipsychotic crossover titrations	
Carbamazepine	Decreased level of ziprasidone[134]	Induction of P450 3A4 by carbamazepine[26, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
MAOIs	n/a	Decreased metabolism of serotonin and norepinephrine by MAOIs, combined with ziprasidone's intrinsic serotonergic and noradrenergic reuptake blockade	Central serotonin syndrome and/or hypertensive crisis[229]	Potentially fatal, but a theoretical concern for this combination
Phenytoin	Decreased level of ziprasidone	Induction of P450 3A4 by phenytoin[26, 134, 160, 161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Pimozide	n/a	Synergistic QT prolongation[26]	Increased arrhythmogenic potential	Theoretical concern
TCAs	n/a	Synergistic QT prolongation[26, 243]	Increased arrhythmogenic potential	Theoretical concern
Typical antipsychotics	n/a	Synergistic QT prolongation with chlorpromazine, mesoridazine, or thioridazine[26]	Increased arrhythmogenic potential	Theoretical concern

APPENDIX 3. Significant Drug-Drug Interactions Involving Mood Stabilizers

Mood Stabilizer and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Carbamazepine				
Aripiprazole	Decreased level of aripiprazole[118]	Induction of P450 3A4 by carbamazepine[118, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
Bupropion	Decreased level of bupropion[192, 193]	Induction of P450 2B6 by carbamazepine[83, 147]	Possible loss of therapeutic efficacy	
Citalopram, escitalopram	Decreased levels of citalopram and escitalopram[196]	Induction of P450 3A4 by carbamazepine[32, 33, 37, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
Clozapine	Decreased level of clozapine[214, 244, 245]	Induction of P450 1A2, 2C9, 3A4, and uridine 5′-diphosphate glucuronosyltransferase(UGT) 1A4 by carbamazepine[43, 50, 123–125, 134, 137, 145, 146, 148, 149, 197, 198]	Possible loss of therapeutic efficacy	Synergistic risk of blood dyscrasias (agranulocytosis from clozapine and aplastic anemia from carbamazepine)[246]
Duloxetine	Decreased level of duloxetine	Induction of P450 1A2 by carbamazepine[37, 146]	Possible loss of therapeutic efficacy	Theoretical concern
Fluoxetine	Increased level of carbamazepine[199]	Inhibition of both multiple P450 enzymes (3A4, 1A2, 2B6, 2C9)[41–43, 46, 60, 135, 200] and P-glycoprotein[47, 138] by fluoxetine plus norfluoxetine	Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.	
Fluvoxamine	1) Increased level of carbamazepine[211, 212] and 2) decreased level of fluvoxamine	1) Inhibition of multiple P450 enzymes (3A4, 1A2, 2B6, 2C9)[42, 43, 45, 48, 50, 51, 135, 200] and P-glycoprotein[47, 52, 138] by fluvoxamine; 2) induction of P450 1A2 by carbamazepine[48, 146]	Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.	The decrease in fluvoxamine levels is a theoretical concern
Haloperidol, mirtazapine	Decreased level of haloperidol or mirtazapine[230, 244, 248, 249]	Induction of P450 1A2 and 3A4 by carbamazepine[88, 89, 114, 134, 137, 145, 146, 149, 197, 198]	Possible loss of therapeutic efficacy	
Lamotrigine	1) Decreased level of lamotrigine[137, 149] and 2) possible increase in level of carbamazepine-10,11-epoxide[260]	1) Induction of UGT 1A4 by carbamazepine[22, 23, 149]; 2) mechanism unknown	1) Possible loss of therapeutic efficacy; 2) possible ataxia, nausea, sedation, confusion, dysarthria, diplopia, tremor, etc.	The increase in carbamazepine-10,11-epoxide with this combination is controversial; one study suggested this increase occurs, and others suggested no such increse[260–263]
Mirtazapine	Decreased level of haloperidol or mirtazapine[230, 244, 248, 249]	See information for interaction of carbamazepine with haloperidol, mirtazapine	Possible loss of therapeutic efficacy	
Nefazodone	1) Increased level of carbamazepine and 2) decreased level of nefazodone[232]	1) Inhibition of P450 3A4 by nefazodone[46, 100, 135, 200]; 2) induction of P450 3A4 by carbamazepine[97, 134, 137, 145, 197, 198]	1) Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.; 2) likely loss of therapeutic efficacy	
Olanzapine	Decreased level of olanzapine[252, 253]	Induction of P450 1A2 and UGT 1A4 by carbamazepine[22, 23, 127, 146, 149]	Possible loss of therapeutic efficacy	
Phenytoin	1) Decreased level of carbamazepine[137, 143] and 2) reported increased level of phenytoin[141, 143]	1) Induction of P450 2B6, 2C9, and 3A4 by phenytoin[135, 147, 159–161, 198, 200]; 2) inhibition of P450 2C19 by carbamazepine[68, 141, 156]	1) Possible loss of therapeutic efficacy; 2) possible nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.	Although there is evidence supporting the increase in phenytoin levels that occurs with this combination, both the carbamazepine and phenytoin package inserts mention possible decreases in phenytoin levels due to induction. It is also unclear how carbamazepine's 2C19 inhibition could overcome its 2C9 induction to produce elevated phenytoin levels. Carbamazepine's activity at P450 2C8/9 and 2C19 is not yet completely understood
Pimozide	Decreased level of pimozide	Induction of P450 1A2 and 3A4 by carbamazepine[117, 134, 137, 145, 146, 197, 198]	Possible loss of therapeutic efficacy	Theoretical concern

Quetiapine	1) Decreased level of quetiapine[129, 254] and 2) increased level of carbamazepine-10,11-epoxide[255]	1) Induction of P450 3A4 by carbamazepine[128, 129, 134, 137, 145, 197, 198]; 2) mechanism unknown (possibly inhibition of epoxide hydrolase)	1) Possible (or even likely) loss of therapeutic efficacy; 2) possible ataxia, nausea, sedation, confusion, dysarthria, diplopia, tremor, etc.	
Risperidone	Decreased level of risperidone[257–259]	Induction of P450 3A4 by carbamazepine[130, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
Sertraline	Decreased level of sertraline[237]	Induction of P450 2B6, 2C9, and 3A4 by carbamazepine[43, 56, 57, 134, 137, 145, 147, 148, 197, 198]	Possible loss of therapeutic efficacy	
Tricyclic antidepressants (TCAs)	1) Decreased levels of TCAs[195, 241], 2) except for the level of clomipramine, which is reportedly increased[142]	1) Induction of P450 1A2, 2C9, and 3A4 and UGT 1A4 by carbamazepine[37, 43, 74–76, 78, 134, 137, 145, 146, 148, 149, 197, 198]; 2) inhibition of P450 2C19 by carbamazepine[75, 141]	Possible loss of therapeutic efficacy	It is confusing that the level of amitriptyline, which also relies strongly on P450 2C19 for its metabolism, should be reliably decreased by carbamazepine[195] and that the level of clomipramine is reportedly increased. Carbamazepine's activity at P450 2C8/9 and 2C19 is not yet completely understood
Topiramate	1) Decreased level of topiramate[163, 264] and 2) possible decreased level of carbamazepine	1) Induction of phase II metabolism by carbamazepine (possibly at UGT 1A4)[149, 163, 164, 265]; 2) induction (mild) of P450 3A4 by topiramate[135, 167, 168, 200]	Possible loss of therapeutic efficacy	Result #2 is a theoretical concern
Typical antipsychotics (general)	Decreased levels of typical antipsychotics[244]	Induction of P450 1A2, 3A4, and UGT 1A4 by carbamazepine[23, 79, 103, 107, 108, 114, 117, 134, 137, 145, 146, 149, 197, 198, 210]	Possible loss of therapeutic efficacy	
Valproate	1) Decreased level of valproate[172, 174, 175, 266], 2) increased production of the hepatotoxic 4-ene-valproate metabolite[172, 267], and 3) increased level of carbamazepine-10,11-epoxide[137]	1) Induction of phase II metabolism by carbamazepine[149, 171]; 2) induction of P450 2C9 (likely) by carbamazepine[43, 148, 170]; 3) inhibition of epoxide hydrolase by valproate[137, 268]	1) Possible loss of therapeutic efficacy; 2) transaminase elevations or even frank hepatitis; 3) possible ataxia, nausea, sedation, confusion, dysarthria, diplopia, tremor, etc.	
Ziprasidone	Decreased level of ziprasidone[134]	Induction of P450 3A4 by carbamazepine[26, 134, 137, 145, 197, 198]	Possible loss of therapeutic efficacy	
Lamotrigine				
Carbamazepine	1) Decreased level of lamotrigine[137, 149] and 2) possible increase in level of carbamazepine-10,11-epoxide[260]	1) Induction of UGT 1A4 by carbamazepine[22, 23, 149]; 2) mechanism unknown	1) Possible loss of therapeutic efficacy; 2) possible ataxia, nausea, sedation, confusion, dysarthria, diplopia, tremor, etc.	The increase in carbamazepine-10,11-epoxide with this combination is controversial; one study suggested this increase occurs, and others suggested no such increase[260–263]
Oxcarbazepine	Decreased level of lamotrigine[154]	Induction of UGT 1A4 by oxcarbazepine[22, 23, 154]	Possible loss of therapeutic efficacy	
Phenytoin	Decreased level of lamotrigine[149, 269]	Induction of UGT 1A4 by phenytoin[149, 269]	Possible loss of therapeutic efficacy	
Sertraline	Increased level of lamotrigine[62]	Inhibition of UGT 1A4 by sertraline[22, 23, 62]	Increased somnolence, confusion, and increased risk of emergence of rash	Lamotrigine level can double with this combination. Risk of rash and risk of progression to Stevens-Johnson syndrome or toxic epidermal necrolysis exist with this combination[150, 151]
Valproate	1) Increased level of lamotrigine[149, 154, 269] and 2) mild (about 25%) decrease in valproate levels[151]	1) Inhibition of UGT 1A4 by valproate[149, 154, 268, 269]; 2) likely mild phase II induction by lamotrigine[151, 171]	1) Increased somnolence, confusion, and increased risk of emergence of rash; 2) possible loss of therapeutic efficacy	1) Lamotrigine level typically doubles with this combination. Risk of rash and risk of progression to Stevens-Johnson syndrome or toxic epidermal necrolysis exist with this combination[150, 151]; 2) theoretical concern

APPENDIX 3. Significant Drug-Drug Interactions Involving Mood Stabilizers (*continued*)

Mood Stabilizer and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Oxcarbazepine				
Lamotrigine	Decreased level of lamotrigine[154]	Induction of UGT 1A4 by oxcarbazepine[22, 23, 154]	Possible loss of therapeutic efficacy	
Phenytoin	1) Increased level of phenytoin[141] and 2) decreased level of oxcarbazepine[269, 270]	1) Inhibition of P450 2C19 by oxcarbazepine[141]; 2) induction of phase II metabolism by phenytoin[149, 162]	1) Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.; 2) possible loss of therapeutic efficacy	
Topiramate	Decreased level of topiramate[265]	Induction of phase II metabolism by oxcarbazepine[154]	Possible loss of therapeutic efficacy	
Phenytoin				
Aripiprazole	Decreased level of aripiprazole	Induction of P450 3A4 by phenytoin[118, 160, 161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Bupropion	Decreased level of bupropion	Induction of P450 2B6 by phenytoin[83, 147]	Possible loss of therapeutic efficacy	Theoretical concern, but likely
Carbamazepine	1) Decreased level of carbamazepine[137, 143] and 2) reported increased level of phenytoin[141, 143]	1) Induction of P450 2B6, 2C9, and 3A4 by phenytoin[135, 147, 159–161, 198, 200]; 2) inhibition of P450 2C19 by carbamazepine[68, 141, 156]	1) Possible loss of therapeutic efficacy; 2) possible nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.	Although there is evidence supporting the increase in phenytoin levels that occurs with this combination, the carbamazepine package insert notes possible decreases in phenytoin levels due to induction. It is also unclear how carbamazepine's 2C19 inhibition could overcome its 2C9 induction to produce elevated phenytoin levels. Carbamazepine's activity at P450 2C8/9 and 2C19 is not yet completely understood
Citalopram, escitalopram	Decreased levels of citalopram and escitalopram	Induction of P450 3A4 and 2C19 by phenytoin[32, 33, 159–161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Clozapine	Decreased level of clozapine[247]	Induction of P450 2C9/19, 3A4, and UGT 1A4 by phenytoin[50, 123–125, 149, 159–161, 198]	Possible loss of therapeutic efficacy	
Fluoxetine, fluvoxamine	Increased level of phenytoin[204, 221, 222]	Inhibition of both P450 2C9/19[43, 44, 68, 155, 156] and P-glycoprotein[47, 158] by fluoxetine plus norfluoxetine and by fluvoxamine[45, 48, 51, 52]	Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.	
Fluvoxamine	Increased level of phenytoin[204, 221, 222]	See information for interaction of phenytoin with fluoxetine, fluvoxamine	Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.	
Haloperidol, mirtazapine	Decreased level of haloperidol or mirtazapine[231, 251]	Induction of P450 3A4 (and possibly pertinent phase II enzymes) by phenytoin[88, 89, 149, 160–162, 198]	Possible loss of therapeutic efficacy	
Lamotrigine	Decreased level of lamotrigine[149, 269]	Induction of UGT 1A4 by phenytoin[149, 269]	Possible loss of therapeutic efficacy	
Mirtazapine	Decreased level of haloperidol or mirtazapine[231, 251]	See information for interaction of phenytoin with haloperidol, mirtazapine	Possible loss of therapeutic efficacy	
Nefazodone	Decreased level of nefazodone	Induction of P450 3A4 by phenytoin[97, 161, 198]	Likely loss of therapeutic efficacy	Theoretical concern, but likely
Olanzapine	Decreased level of olanzapine	Induction of UGT 1A4 by phenytoin[22, 23, 149]	Possible loss of therapeutic efficacy	Theoretical concern, but likely
Oxcarbazepine	1) Increased level of phenytoin[141] and 2) drecreased level of oxcarbazepine[269, 270]	1) Inhibition of P450 2C19 by oxcarbazepine,[68, 141, 156]; 2) induction of phase II metabolism by phenytoin[149, 162]	1) Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.; 2) possible loss of therapeutic efficacy	
Pimozide	Decreased level of pimozide	Induction of P450 3A4 by phenytoin[117, 160, 161, 198]	Possible loss of therapeutic efficacy	Theoretical concern

Quetiapine	Decreased level of quetiapine[256]	Induction of P450 3A4 by phenytoin[128, 129, 160, 161, 198]	Likely loss of therapeutic efficacy	This combination produces a fivefold increase in the clearance of quetiapine
Risperidone	Decreased level of risperidone[130]	Induction of P450 3A4 by phenytoin[130, 160, 161, 198]	Possible loss of therapeutic efficacy	
Sertraline	Decreased level of sertraline[237]	Induction of P450 2B6, 2C9/19, and 3A4 by phenytoin[56, 57, 147, 159, 161, 198]	Possible loss of therapeutic efficacy	
TCAs	Decreased levels of TCAs	Induction of P450 2C19 and 3A4 and UGT 1A4 by phenytoin[74–76, 78, 149, 159–161, 198]	Possible loss of therapeutic efficacy	Theoretical concern, but likely
Topiramate	1) Increased level of phenytoin[271] and 2) decreased level of topiramate[163, 166, 264, 265, 271]	1) Inhibition of P450 2C19 by topiramate[68, 156, 167, 268]; 2) induction of phase II metabolism by phenytoin[149, 162–164]	1) Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.; 2) possible loss of therapeutic efficacy	
Typical antipsychotics (general)	Decreased levels of typical antipsychotics[251]	Induction of P450 3A4 and UGT 1A4 by phenytoin[79, 106, 109, 149, 160, 161, 198]	Possible loss of therapeutic efficacy	
Valproate	1) Increased ''total'' levels of phenytoin, with a disproportionate increase in the free fraction of phenytoin[175, 272, 273], 2) decreased level of valproate[172], and 3) increased production of the hepatotoxic 4-ene-valproate metabolite[172, 267]	1) Inhibition of P450 2C9[173], combined with displacement from plasma protein binding sites[272], by valproate[148, 155, 156]; 2) induction of P450 2C9/19 and phase II metabolism by phenytoin[149, 159, 162, 170, 171]; 3) induction of P450 2C9 (likely) by phenytoin[159, 170]	1) Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.; 2) possible loss of therapeutic efficacy; 3) transaminase elevations or even frank hepatitis	With this combination, the patient's free phenytoin level (as opposed to a total level) should be checked[273]. It is generally not necessary to check a free valproate level when valproate is combined with phenytoin
Ziprasidone	Decreased level of ziprasidone	Induction of P450 3A4 by phenytoin[26, 134, 160, 161, 198]	Possible loss of therapeutic efficacy	Theoretical concern
Topiramate				
Carbamazepine	1) Decreased level of topiramate[163, 264] and 2) possible decreased level of carbamazepine	1) Induction of phase II metabolism by carbamazepine (possibly at UGT 1A4)[149, 163, 164, 265]; 2) induction (mild) of P450 3A4 by topiramate[135, 167, 168, 200]	Possible loss of therapeutic efficacy	Result #2 is a theoretical concern
Oxcarbazepine	Decreased level of topiramate[265]	Induction of phase II metabolism by oxcarbazepine[154]	Possible loss of therapeutic efficacy	
Phenytoin	1) Increased level of phenytoin[271] and 2) decreased level of topiramate[163, 166, 264, 265, 271]	1) Inhibition of P450 2C19 by topiramate[68, 156, 167, 268]; 2) induction of phase II metabolism by phenytoin[149, 162–164]	1) Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.; 2) possible loss of therapeutic efficacy	
Valproate				
Carbamazepine	1) Decreased level of valproate[172, 174, 175, 266], 2) increased production of the hepatotoxic 4-ene-valproate metabolite[172, 267], and 3) increased level of carbamazepine-10,11-epoxide[137]	1) Induction of phase II metabolism by carbamazepine[149, 171]; 2) induction of P450 2C9 (likely) by carbamazepine[43, 148, 170]; 3) inhibition of epoxide hydrolase by valproate[137, 268]	1) Possible loss of therapeutic efficacy; 2) transaminase elevations or even frank hepatitis; 3) possible ataxia, nausea, sedation, confusion, dysarthria, diplopia, tremor, etc.	
Lamotrigine	1) Increased level of lamotrigine[149, 154, 269], and 2) mild (about 25%) decrease in valproate levels[151]	1) Inhibition of UGT 1A4 by valproate[149, 154, 268, 269]; 2) likely mild phase II induction by lamotrigine[151, 171]	1) Increased somnolence, confusion, and increased risk of emergence of rash; 2) possible loss of therapeutic efficacy	1) Lamotrigine level typically doubles with this combination. Risk of rash and risk of progression to Stevens-Johnson syndrome or toxic epidermal necrolysis exist with this combination[150, 151]; 2) theoretical concern
Phenytoin	1) Increased ''total'' levels of phenytoin, with a disproportionate increase in the free fraction of phenytoin[175, 272, 273], 2) decreased level of valproate[172], and 3) increased production of the hepatotoxic 4-ene-valproate metabolite[172, 267]	1) Inhibition of P450 2C9[173], combined with displacement from plasma protein binding sites[272], by valproate[148, 155, 156]; 2) induction of P450 2C9/19 and phase II metabolism by phenytoin[149, 159, 162, 170, 171]; 3) induction of P450 2C9 (likely) by phenytoin[159, 170]	1) Nystagmus, ataxia, nausea, sedation, dysarthria, tremor, etc.; 2) possible loss of therapeutic efficacy; 3) transaminase elevations or even frank hepatitis	With this combination, the patient's free phenytoin level (as opposed to a total level) should be checked[273]. It is generally not necessary to check a free valproate level when valproate is combined with phenytoin

APPENDIX 4. Significant Drug-Drug Interactions Involving Other Psychotropic Agents and Nonpsychotropic Agents

Index Drug and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Alprazolam (metabolized by P450 3A4)				
Carbamazepine	Decreased level of alprazolam[145]	Induction of P450 3A4 by carbamazepine[134, 137, 145, 197, 274]	Possible loss of therapeutic efficacy	
Clarithromycin, erythromycin	Increased level of alprazolam[274]	Inhibition of P450 3A4 by clarithromycin andy by erythromycin[186, 274–276]	Increased somnolence	
Fluoxetine, fluvoxamine	Increased level of alprazolam[217, 277]	Inhibition of P450 3A4 by fluoxetine and by fluvoxamine[45, 46, 50, 274]	Increased somnolence	
Nefazodone	Increased level of alprazolam[96, 100]	Inhibition of P450 3A4 by nefazodone[46, 100, 186, 274]	Increased somnolence	
Phenytoin	Decreased level of alprazolam	Induction of P450 3A4 by phenytoin[160, 161, 274]	Possible loss of therapeutic efficacy	Theoretical concern
St. John's wort	Decreased level of alprazolam[278, 279]	Induction of P450 3A4 by St. John's wort[274, 278–280]	Possible loss of therapeutic efficacy	
Aspirin				
Valproate	Increased level of ''free'' or unbound valproate[29, 30, 281]	Plasma protein binding displacement of valproate and inhibition of β-oxidation by aspirin[29, 30, 172, 182]	Somnolence, confusion, incoordination, nausea, vomiting, etc.	The patient's free valproate level (versus a total level) should be checked when valproate is combined with even moderate doses of aspirin (325 mg/day or more)
Buspirone (metabolized by P450 3A4)				
Carbamazepine	Decreased level of buspirone[282]	Induction of P450 3A4 by carbamazepine[134, 137, 145, 197, 275, 282]	Possible loss of therapeutic efficacy	Theoretical concern[283]
Clarithromycin, erythromycin	Increased level of buspirone[275, 284]	Inhibition of P450 3A4 by clarithromycin and by erythromycin[186, 275, 276, 282]	Increased somnolence, headache, nausea, etc.	
Grapefruit juice	Increased level of buspirone[285]	Inhibition of P450 3A4 (in the gut) by grapefruit juice[186, 275, 282, 285, 286]	Increased somnolence, headache, nausea, etc.	
Monoamine oxidase inhibitors (MAOIs)	n/a	Decreased metabolism of serotonin combined with partial serotonin agonism by buspirone	Central serotonin syndrome and/or hypertensive crisis[18, 19, 282]	
Nefazodone	Increased level of buspirone[282]	Inhibition of P450 3A4 by nefazodone[46, 100, 186, 275, 282]	Increased somnolence, headache, nausea, etc.	
Phenytoin	Decreased level of buspirone[282]	Induction of P450 3A4 by phenytoin[160, 161, 275, 282]	Possible loss of therapeutic efficacy	Theoretical concern[283]
St. John's wort	Decreased level of buspirone	Induction of P450 3A4 by St. John's wort[275, 278–280]	Possible loss of therapeutic efficacy	Theoretical concern; central serotonin syndrome has been reported with this combination.[278]
Caffeine (metabolized by P450 1A2)				
Clozapine	Increased level of clozapine[287–289]	Inhibition of P450 1A2 by caffeine[50, 123, 289, 290]	Sedation, constipation, blurry vision, hypersalivation, etc.	Although this combination typically raises clozapine levels by only about 25%, this effect, and/or its discontinuation, can be important for individual patients
Fluvoxamine	Increased level of caffeine[48]	Inhibition of P450 1A2 by fluvoxamine[48, 289, 290]	Agitation, anxiety, tachycardia, excessive diuresis, etc.	
Lithium	Decreased level of lithium[291, 292]	Increased renal excretion of lithium caused by caffeine[293]	Possible loss of therapeutic efficacy	

Ethinylestradiol (metabolized by P450 3A4)				
Carbamazepine	Decreased level of ethinylestradiol[197, 294]	Induction of P450 3A4 by carbamazepine[134, 137, 145, 197, 295]	Unintended pregnancy, breakthrough bleeding, etc.	
Lamotrigine	Decreased level of lamotrigine[296, 297]	Induction of UGT 1A4 by ethinlyestradiol[22, 23, 296, 297]	Possible loss of therapeutic efficacy	This combination typically produces a 50% decrease in lamotrigine levels
Oxcarbazepine	Decreased level of ethinylestradiol[153, 294, 298, 299]	Induction of P450 3A4 by oxcarbazepine[153, 295]	Unintended pregnancy, breakthrough bleeding, etc.	
Phenytoin	Decreased level of ethinylestradiol[197, 294]	Induction of P450 3A4 by phenytoin[160, 161, 295]	Unintended pregnancy, breakthrough bleeding, etc.	
St. John's wort	Decreased level of ethinylestradiol[278, 280, 300]	Induction of P450 3A4 by St. John's wort[278–280, 295]	Unintended pregnancy, breakthrough bleeding, etc.	
Topiramate	Decreased level of ethinylestradiol[169, 294, 299]	Induction of P450 3A4 by topiramate[168, 295]	Unintended pregnancy, breakthrough bleeding, etc.	
Grapefruit juice				
Buspirone	Increased level of buspirone[285]	Inhibition of P450 3A4 (in the gut) by grapefruit juice[186, 275, 285, 286]	Increased somnolence, headache, nausea, etc.	
Carbamazepine	Increased level of carbamazepine[301]	Inhibition of P450 3A4 (in the gut) > 1A2 and P-glycoprotein by grapefruit juice[135, 138, 285, 286, 302–304]	Ataxia, nausea, sedation, dysarthria, diplopia, tremor, etc.	
Pimozide	Increased level of pimozide	Inhibition of P450 3A4 (in the gut) >1A2 by grapefruit juice[285, 286, 303, 304]	Increased extrapyramidal symptoms and arrhythmogenic potential	Theoretical concern[186, 233]
Hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors ("statins"), specifically atorvastatin, lovastatin, and simvastatin (metabolized by P450 3A4)				
Carbamazepine	Decreased "statin" blood level[144]	Induction of P450 3A4 by carbamazepine[134, 137, 145, 197, 305, 306]	Possible loss of therapeutic efficacy	
Grapefruit juice, nefazodone	Increased "statin" blood level[286, 305, 307–309]	Inhibition of P450 3A4 (in the gut) by grapefruit juice or nefazodone[46, 100, 186, 285, 286, 305, 306]	Increased risk of rhabdomyolysis and associated symptoms (fatigue, myalgias, etc.)	
Nefazodone	Increased "statin" blood level[286, 305, 307–309]	See information for interaction of HMG-CoA reductase inhibitors with grapefruit juice, nefazodone	Increased risk of rhabdomyolysis and associated symptoms (fatigue, myalgias, etc.)	
Phenytoin	Decreased "statin" blood level[306]	Induction of P450 3A4 by phenytoin[160, 161, 305, 306]	Possible loss of therapeutic efficacy	
St. John's wort	Decreased "statin" blood level[280, 310]	Induction of P450 3A4 and P-glycoprotein by St. John's wort[278–280, 305, 306]	Possible loss of therapeutic efficacy	
Lithium				
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists	Increased lithium level[28, 311–313]	Decreased renal excretion of lithium caused by ACE inhibitors and angiotensin II receptor antagonists	Dizziness, blurry vision, tremor, nausea, vomiting, confusion, etc.	
Loop diuretics	Variable or no change in lithium levels[27]	Unclear	Unclear	This effect is unpredictable; monitoring of lithium level is advised

APPENDIX 4. Significant Drug-Drug Interactions Involving Other Psychotropic Agents and Nonpsychotropic Agents (*continued*)

Index Drug and Interacting Drug	Pharmacokinetic Results	Mechanisms	Clinical Consequences	Comments
Nonsterioidal anti-inflammatory drugs (NSAIDs), except aspirin and sulindac	Increased lithium level[28, 314]	Decreased renal excretion of lithium caused by NSAIDs	Dizziness, blurry vision, tremor, nausea, vomiting, confusion, etc.	This effect can be quite variable in magnitude, from minimal changes to doubling or even greater changes in lithium levels. Close monitoring of lithium level is advised
Osmotic diuretics and xanthines	Decreased level of lithium[28, 291, 292]	Increased renal excretion of lithium caused by osmotic diuretics and xanthines[293, 315]	Possible loss of therapeutic efficacy	
Thiazide and potassium-sparing diuretics, except amiloride	Increased lithium level[27, 28]	Decreased renal excretion of lithium caused by thiazide and potassium-sparing diuretics, except amiloride[316]	Dizziness, blurry vision, tremor, nausea, vomiting, confusion, etc.	
St. John's wort				
Alprazolam	Decreased level of alprazolam[278, 279]	Induction of P450 3A4 by St. John's wort[274, 278–280]	Possible loss of therapeutic efficacy	
Buspirone	Decreased level of buspirone	Induction of P450 3A4 by St. John's wort[275, 278–280]	Possible loss of therapeutic efficacy	Theoretical concern; central serotonin syndrome has been reported with this combination[278]
Ethinylestradiol	Decreased level of ethinylestradiol[278, 280, 300]	Induction of P450 3A4 by St. John's wort[278–280]	Unintended pregnancy, breakthrough bleeding, etc.	
HMG-CoA reductase inhibitors (''statins''), specifically atorvastatin, lovastatin, and simvastatin	Decreased ''statin'' blood level[280, 310]	Induction of P450 3A4 and P-glycoprotein by St. John's wort[278–280, 305, 306]	Possible loss of therapeutic efficacy	
MAOIs	n/a	Decreased metabolism of serotonin by MAOIs, combined with serotonin reuptake inhibition by St. John's wort	Increased risk of central serotonin syndrome[18, 19, 317]	Theoretical concern
Selective serotonin reuptake inhibitors (SSRIs)	n/a	Synergistic serotonin reuptake inhibition	Increased risk of central serotonin syndrome[278, 280, 317]	All combinations of St. John's wort with serotonergically active antidepressants are of theoretical concern, although the same could be said of pharmacokinetically safe combinations of SSRIs with other serotonergically active antidepressants (such as sertraline plus mirtazapine)
Tobacco (smoked)				
Clozapine	Decreased level of clozapine[318–321]	Induction of P450 1A2 by tobacco smoking[123, 124, 322]	Possible loss of therapeutic efficacy	
Fluvoxamine	Decreased level of fluvoxamine[49, 318]	Induction of P450 1A2 by tobacco smoking[48, 49, 322]	Possible loss of therapeutic efficacy	
Olanzapine	Decreased level of olanzapine[253, 318, 321, 323]	Induction of P450 1A2 by tobacco smoking[127, 322]	Possible loss of therapeutic efficacy	
Phenothiazines and most other typical antipsychotics, including haloperidol	Decreased typical antipsychotic levels[103, 318, 322, 324–326]	Induction of P450 1A2 by tobacco smoking[103, 107, 114, 322]	Possible loss of therapeutic efficacy	
Tertiary amine tricyclic antidepressants (TCAs)	Decreased level of tertiary amine TCAs[318, 322]	Induction of P450 1A2 by tobacco smoking[65, 74–76, 322]	Possible loss of therapeutic efficacy	