

Update: Drug-Psychotropic Drug Interactions

This section will appear in the Journal from time to time as new important reports on drug-psychotropic drug interactions are published. Since the authors are not bound by only scientific studies and random control trials, even technical reports from work in progress in laboratories, case reports, and early observations will be included. We welcome the readership to bring to our attention important interactions that we have overlooked and should be considered for citation in this section. It is our hope to move the scope of reporting to include technical reports, Food Drug Administration (FDA) communications, laboratory reports, and so forth, and not limit citations only to refereed journals. Thus, alerts will be more timely and not delayed by publication schedules.

Psychotropic drug versus psychotropic drug—update

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Abstract

Psychotropic drugs are not necessarily the drugs of psychiatry. Seventy percent of antidepressants, and 90% of anxiolytics are prescribed by nonpsychiatric physicians. Since psychotropic medications are so frequently employed by nonpsychiatric physicians, e.g., neurologists, primary care physicians, internists, and because large numbers of their patients are concurrently on medical drugs for somatic reasons, the interactions of psychotropic versus medical drugs and psychotropic versus psychotropic drugs as listed below must be understood before primary care physicians or psychiatrists prescribe psychotropic medications, especially to the medically ill. Seventy commonly prescribed psychotropic drugs were examined for their interactions with other psychotropic medications using six reference tools: 1) MEDLINE (PubMed) employing the first generic psychotropic drug name, the second generic psychotropic drug name, and the term “interaction;” 2) *Hanston’s Drug Interaction Analysis and Management Text* (quarterly updated version) [2]; 3) *Drug Interactions Facts (Facts and Comparisons)* (July 2001 quarterly updated version) [3]; 4) *Micromedex Drug-dex* [4]; 5) *American Hospital Formulary Service Drug Information* [5]; and 6) *Food and Drug Administration (MedWatch)* (Dear Doctor Letters and new labeling) (www.fed.gov/medwatch for (1999, 2000, and 2001). The authors recognized that all of the above sources do not necessarily cover the entire information database regarding drug–drug interactions. (Citations regarding children, reports in foreign languages or concerning food, animals, in vitro experiments, analgesics, and naturalistic—herbal or natural products—treatment interactions were excluded). © 2004 Elsevier Inc. All rights reserved.

1. Introduction

The concomitant use of psychotropic with other psychotropic medications is ubiquitous in the general hospital setting, and in ambulatory practice. The aim of this literature drug–drug interaction analysis is to compare the most commonly prescribed psychotropic medications with other psychotropic drugs and their interactions if they are em-

ployed simultaneously. Furthermore, many of the same drugs are prescribed by other disciplines, e.g., neurology, medicine, geriatrics, but not necessarily for the same disorder, e.g., carbamazepine for seizure (neurology) and mood stabilization (psychiatry). Psychiatrists as well as other disciplines need to be informed of the potential hazards of employing concomitantly diverse psychotropic drugs.

Psychiatrists frequently encounter patients with comorbid psychiatric conditions such as affective disorders or psychosis and delirium and dementia. These patients are often on antidepressants, antipsychotics, mood stabilizers, or combinations of these categories. This may present a

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Table 1
Commonly prescribed psychotropic medications

amantadine	methylphenidate
amitriptyline	molindone
amphetamine	nefazodone
alprazolam	nortriptyline
amobarbital	olanzapine
benztropine	oxazepam
bupropion	pargyline
buspirone	paroxetine
butalbital	pemoline
carbamazepine	perphenazine
choral hydrate	phenobarbital
chlorthalidoxepine	quetiapine
chlorpromazine	risperidone
citalopram	sertindole
clomipramine	sertraline
clonazepam	sildenafil
clozapine	sodium amytal
desipramine	tarcine
dextroamphetamine	temazepam
diazepam	thioridazine
diphenhydramine	thiothixene
divalproex sodium	trazodone
donepezil	tranylcypromine
fluoxetine	triazolam
fluphenazine	trifluoperazine
fluvoxamine	trihexiphenidyl
gabapentin	valproic acid
haloperidol	venlafaxine
imipramine	zaleplon
lamotrigine	zolpidem
lithium	
lorazepam	
loxapine	
meprobamate	

challenge when assessing which psychiatric drugs can be used simultaneously: Which medications are safe to prescribe, which combination of psychotropic drugs would be the most effective, and which would necessitate a dose adjustment from that usually prescribed or more careful monitoring of serum levels than is required if only one medication is applied at a time.

The aim of the study is to describe psychotropic versus psychotropic adverse drug interactions, enumerate the mechanisms of the interactions when possible, and given the adverse interaction and the degree of its severity, specify recommended action(s) for the practitioners.

2. Methods

The drugs selected for review were from: 1) the Redbook list of the 200 most often prescribed medications in the United States; 2) those medications most commonly employed by the Division of Behavioral Medicine and Consultation Psychiatry, and the Department of Pharmacy (Mount Sinai - NYU Medical Center/Health System) (Table 1). The disciplines of the investigators were: pharmacy-drug information (G.C.), psychiatry (J.J.S., N.M.C.), 2 research

assistants (A.K., K.S.), and a medical programmer (J.J.S.) to install the data into a special software program for distribution to consultation—liaison programs throughout the world [1].

The search strategy utilized the following indexing systems: 1) MEDLINE (PubMed) employing the first generic psychotropic drug name, the second generic psychotropic drug name, and the term “interaction;” 2) *Hanston’s Drug Interaction Analysis and Management Text* (quarterly updated version) [2]; 3) *Drug Interactions Facts (Facts and Comparisons)* (July 2001 quarterly updated version) [3]; 4) *Micromedex Drug-dex* [4]; 5) *American Hospital Formulary Service Drug Information* [5]; and 6) *Food and Drug Administration (MedWatch)* (Dear Doctor Letters and new labeling) (www.fed.gov/medwatch for (1999, 2000, and 2001). The authors recognized that all of the above sources do not necessarily cover the entire information database regarding drug–drug interactions. (Citations regarding children, reports in foreign languages or concerning food, animals, in vitro experiments, analgesics, and naturalistic—herbal or natural products—treatment interactions were excluded).

Should one utilize the known mechanism(s) of interaction and established pharmacokinetics and pharmacologic principles to extrapolate selectively to other drugs in a given class for which the given interaction has not been reported? For example, interactions involving SSRIs were generalized when the risk for the occurrence of the serotonin syndrome could be based on a potential pharmacological interaction. For interactions that were pharmacokinetic in nature, differences in extreme impact were addressed individually. Similarity of action in a particular enzyme system might indicate possible interactions. Nefazodone is a known inhibitor of the cytochrome P3A4 isoenzyme. Yet, its use with cisapride was initially not contraindicated. Cisapride is a known and established cytochrome P3A4 substrate that could produce cardiac arrhythmias and/or death when prescribed with cytochrome P3A4 inhibitors. Judicious practice would have questioned the use of nefazodone with cisapride despite the lack of a documented interaction. Eventually, the prescription of cisapride was officially contraindicated with nefazodone.

3. Dynamics of drug–drug interaction

Although the dynamics of drug–drug interaction(s) have been described before [1], it is important to review them here as the psychotropic drug—psychotropic drug interaction summaries which follow are constructed with this algorithm in mind and a reader may not have access to the previous communication. “It is necessary to determine the circumstances in which drugs might interact, and when the clinical situation would be protective or aversive, by adding or subtracting Drug A to or from Drug B, and vice versa. For example, if Drug A and Drug B were started simulta-

Table 2
Drug interactions: adding drugs

Patient is on		Add on	
A	(Drug A alters metabolism of Drug B)	B	No impact as the effect of A on B will be accounted for as B is initiated.
A&B	“		No action is necessary if there are no adverse effects present, the patient is stable on both and the interaction is accounted for.
B	“	A	Dose of B may need to be adjusted as the effect of A on B is observed.

neously and Drug A had the potential to alter the metabolism of Drug B, regularly monitoring the clinical response may be protective in that the net effect of the interaction could be adjusted for as the clinician treated the patient either until improvement or toxicity.

Adding Drug A to Drug B where Drug A alters the metabolism of Drug B, might change (increase/decrease) the concentration of B, which is already in the patient's system, and initiate an adverse drug response. Before adding A, drug B might have been at a stable therapeutic dose. Three situations may prevail: higher serum concentration of B, less of B, or thirdly, a pharmacologic or pharmacodynamic interaction with an additive incidence or severity of an adverse event. On the other hand, adding Drug B to a steady state of Drug A, where Drug A alters the metabolism of Drug B but Drug A is not affected by Drug B, will not be aversive, as the clinician may add more or less of Drug B, depending upon the clinical situation. Thus the clinician can compensate for the interaction by adjusting the dose of Drug B. An approach to observing drug–drug interactions is to outline Drug A's impact on Drug B when adding and subtracting one drug to or from the other (see Table 2).

Removing Drug A from Drug B or Drug B from Drug A, where Drug A alters metabolism of Drug B, presents additional issues: Discontinuing one drug may raise or lower the concentration of another, may alter the clinical effects of the remaining drug and/or may precipitate toxicity. The practitioner needs to assess the clinical effects of the remaining drug during withdrawal of the second drug (see Table 3).

In the appendix describing the drug interactions, this algorithm is employed to aid the physician when adding or discontinuing drugs, which are known to have adverse reactions.

4. Rating system: significance levels

Most rating systems indicate: 1) major significance; 2) moderate significance; and, 3) minor significance. Signifi-

Table 3
Drug interactions: removing drugs

Patient on		Take away	
A + B	(Drug A alters metabolism of Drug B)	B	No change in the dose of A will be necessary.
A + B	“	A	The dose of B may need to be altered as the effect of A on B dissipates.

cance level 1 indicates a major contraindication or a drug interaction that requires very careful monitoring. The clinician needs to document why he or she is prescribing this combination, and the medical necessity to use both drugs concomitantly only if there is no alternative or the potential benefit outweighs the risk. Drug combinations producing an interaction with a significance level 1 are combinations that result in serious and potentially life threatening adverse effects such as arrhythmia and/or death. Obviously, if this combination is to be used the drug(s) in question must be prescribed with an explanation as to the need for their concomitant use and cautious monitoring. Documentation of the clinician's awareness of the potential serious—level 1—interaction should be accomplished at the time of prescribing this potentially dangerous combination. In addition, it is obligatory to communicate to the other health care providers the potential interactions and adverse outcomes which they should be on guard to observe. Obviously, the optimum choice, if possible, is to use an alternative medication to avoid significance level 1 interactions.

With significance level 2, the potential interaction must also be documented and the clinical outcome(s) must be monitored carefully so that unacceptable, pernicious reactions are halted as soon as possible. If feasible, consideration should be given to an alternative agent that does not share the same interaction potential. It is essential that the clinician document that the potential drug interactions were considered when using this combination. It is also essential to alert the patient's health care providers of the potential interactions so that they are observed early in their course.

Significance level 3 does not preclude the use of a specific drug, but clinical decision making requires acknowledging if the adverse reactions, (e.g., nausea, rash, etc.) might be precluded by choosing an alternative drug. The potential interaction and its mechanism(s) needs documentation in the patient's medical chart and the patient's health care providers need to be informed.

Another rating system is employed by *Drug Interaction Facts* which utilizes a 5 point significance classification schema [3]:

1. **Avoid combination:** risk always outweighs benefit;
2. **Usually avoid combination:** use combination only under special circumstances;

3. **Minimize risk:** take action as necessary to reduce risk;
4. **No action needed:** risk of adverse outcomes appears small; and,
5. **No interaction:** evidence suggests no interaction.

When data were obtained from *Drug Interaction Facts* the 5 point scale was converted to the 3 levels of significance rating system described earlier which is employed in the appendix.

5. Conclusion

We described previously methods to keep abreast of newly reported drug–drug interactions, and identified instruments available to accomplish this task [1]. Each month new drug–drug interactions are described. Psychotropic versus psychotropic drug interactions are less often thought of and considered than medical drug – psychotropic drug. This unfolding of knowledge of psychotropic drug–psychotropic drug interactions illustrates the importance of methods of surveillance to ensure that information is current, accurate, and available. Rosebraught et al. report that medical schools and residency programs should provide more training on preventing adverse drug reactions [11].

Therefore, the data presented in this paper will be available on the internet on a Web site (www.microcares.com), and as a part of the dictionaries in a computerized medical record, MICROCARES, which is currently employed by Consultation-Liaison (C-L) psychiatrists at the interface of medicine and psychiatry in the general acute care inpatient and ambulatory setting. This will permit medical students, house officers, fellows, and attendings in psychiatry, and primary care to have immediate access to this essential drug information as well as to new drug–drug interactions as they are discovered and reported through the variety of resources described above and the safety information maintained by the pharmaceutical manufacturers.

The authors were impressed with the number and severity of drug interactions when 2 or more psychotropic drugs were employed simultaneously. Because many disciplines employ psychotropic drugs, the consultation psychiatrist may encounter the patient who is already on one or more psychotropic drugs. The psychiatrist must be aware of psychotropic–psychotropic interactions when he or she recommends *additional* psychotropic drugs. (Many of these interactions were not found on 2 commonly employed software systems: *Interact* and *ePocrates* [6–8].)

Pharmaceutical companies develop limited drug interaction profiles before the introduction of a new medication. Preclinical in vitro and clinical studies are the basis for this information. After the introduction of a new drug, additional studies are conducted and new drug interaction reports are collected and continuously evaluated. This “from use” data offers a valuable insight into level 1, 2, and 3 significant

interactions and their frequencies. “From use” data may provide early indications of potential drug interactions that have not been previously identified. After evaluation, reports can be the basis for a pharmacokinetic drug–drug interaction study to determine the significance of a collection of single case reports. A well-designed pharmacokinetic drug interaction study can confirm the validity of a group of single case reports. Single case reports were weighted to be less significant than several case reports with similar findings. Well-designed pharmacokinetic studies demonstrating a significant drug interaction were weighted significantly higher in our review than single case reports.

Because the patient is the “guinea pig” for reactions not observed during clinical trials and the FDA approval process, it is this natural experiment of the patient using a drug over time, using the medication with other drugs, herbal agents, and foods, and in some cases acquiring additional medical illness, etc., which provide the matrix for the interactions to occur. Such data could compare and counter that presented in “Prozac Backlash” in which the author argues that long term effects of the SSRIs can be injurious to brain, memory, motor movements functioning, etc [9]. The Eli Lilly Co. has use data from over 20 million initial and renewal prescriptions of fluoxetine (1986–2001) which might answer some of these questions. They probably can never have a definitive statement about all adverse responses, because many are not reported, and many reported are not necessarily related to the drug or drugs in question. Unfortunately, the reports received by the manufacturer may be self-report statements not verified by a physician.

It would be important to know about the long term use of medication, gender issues and age considerations. Health care workers might also know if the frequency of adverse reactions is rare, occasional or frequent. And, such “use data” can illuminate risk characteristics for adverse drug responders, e.g., the elderly, women, those with heart disease, diabetes, etc., to guide the physician and the patient with regard to the risk versus benefit from combined medication usage.

Medical drugs are not tested against psychotropics drugs before they are FDA approved. Nor are psychotropics drugs tested against other psychotropics medications before they are approved. Some combinations may not have been used, reported, or catalogued as yet. As one follows the evolution of antipsychotic medications from reserpine (1940s), chlorpromazine (1950s), haloperidol, fluphenazine, thioridazine (1960s), to the atypical antipsychotics (loxapine, risperidone, olanzapine, quetiapine (1990s), and finally to the “atypical atypicals” (ziprasidone, aripiprazole, iloperidone (2000) [10], it is understandable that we need to wait and see what happens with these 21st century medications with regard to drug–drug interactions. There has not been sufficient time for the “atypical atypicals” to run the “natural experiment” and be sufficiently employed by the human “guinea pig” with a variety of medical illnesses, medical drugs, and psychotropic medications to know their poten-

tially significant adverse interactions. Finally, chronic medication use versus acute concomitantly administered drugs has not been delineated. Clinical trials to determine psychotropic drug interactions with other psychotropic medications would be unethical and could unnecessarily harm a patient. Drug manufacturers often debate or discount the adverse side effects of their medications [12].

Psychotropic drugs are not necessarily the drugs of psychiatry. Seventy percent of antidepressants, and 90% of anxiolytics are prescribed by non psychiatric physicians. Since psychotropic medications are so frequently employed by non psychiatric physicians, e.g., neurologists, primary care physicians, internists, and since large numbers of their patients are concurrently on medical drugs for somatic reasons, the interactions listed below must be understood before primary care physicians or psychiatrists prescribe psychotropic medications, especially to the medically ill.

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Appendix 1. Psychotropic and psychotropic drug interactions

Alprazolam, Midazolam/Carbamazepine

Significance level 2: Moderate

Advice to Practitioner: Carbamazepine can increase the metabolism of some benzodiazepines (alprazolam and midazolam). Interactions of this type may take some time to occur or dissipate. If a patient is on carbamazepine and a benzodiazepine is added, no intervention is required, as the dose of the benzodiazepine will be monitored by clinical efficacy. If a patient is stabilized on the combination, no action is necessary. If a patient is on a benzodiazepine and carbamazepine is added, decreased benzodiazepine activity may be seen. Increased doses may be needed.

Action: Monitor benzodiazepine efficacy and adjust dose as needed as indicated above. An unaffected benzodiazepine may also be used.

Alprazolam, Midazolam, Triazolam/Selective Serotonin Reuptake Inhibitors (SSRI) (Fluoxetine, Fluvoxamine):

Significant level 2: Moderate

Advice to the Practitioner: Fluoxetine and fluvoxamine inhibit CYP450 3A4 which metabolizes alprazolam, midazolam, and triazolam. Interactions of this type may take some time to onset or dissipate. If a patient is on alprazolam,

and any of the above named agents are added, increased benzodiazepine activity may be seen. If a patient is stabilized on the combination, no action is necessary. If a patient is on either fluoxetine or fluvoxamine and alprazolam, midazolam or triazolam is added, no action is necessary, as the dose of above benzodiazepine will be determined by clinical efficacy.

Action: Monitor for signs of benzodiazepines efficacy and adjust dose as indicated above. Consider switching to a benzodiazepine eliminated by glucuronidation (lorazepam, oxazepam, temazepam) and or, an alternative SSRI (paroxetine) may be considered.

Amantadine/Anticholinergics (Benztropine, Trihexyphenidyl)

Significance level 3: Minor

Advice to Practitioner: Amantadine has anticholinergic effects. When used with other agents that have anticholinergic effects, increased anticholinergic and central nervous system (CNS) effects may occur. This interaction may be a concern in patients on high doses of these agents. In a patient on an anticholinergic agent, increased anticholinergic effects should be expected when Amantadine is added. No action is necessary if a patient is already maintained on the 2 agents. If an anticholinergic agent is being added to Amantadine, increased anticholinergic effects should be expected.

Action: Consider decreasing the dose of the anticholinergic agent if side effects become problematic.

Amantadine/Thioridazine

Significance level 3: Minor

Advice to the Practitioner: In elderly patients, with Parkinsonian Syndrome, thioridazine has been associated with increased tremor when added to Amantadine. This has not been seen with other phenothiazines. Patients should be informed of this possibility and alternative phenothiazines or other antipsychotics used if it is problematic.

Action: Educate and monitor patient for increase tremor.

Amantadine/Tricyclic Antidepressants (TCA)

Significance level 3: Minor

Advice to the Practitioner: Amantadine has anticholinergic effects. When used with a TCA, especially those with high anticholinergic effects, increased anticholinergic and effects may occur. This interaction may be a concern in patients on high doses of these agents. In a patient on a TCA, increased anticholinergic effects should be expected when Amantadine is added. No action is necessary if a patient is already maintained on the 2 agents. If a TCA is being added to Amantadine, increased anticholinergic effects should be expected.

Action: Use a TCA with lower anticholinergic activity or from another class of antidepressant with Amantadine if anticholinergic effects are potentially problematic.

Amitriptyline, Imipramine, Nortriptyline/Verapamil Significance level 3: Minor

Advice to the Practitioner: A controlled study has shown that verapamil decreases amitriptyline, imipramine and nortriptyline clearance by 25%. The addition of verapamil to amitriptyline, imipramine, or nortriptyline may lead to toxicity (arrhythmia, dry mouth sedation, and urinary retention). When verapamil is given to a patient stable on amitriptyline, imipramine, or nortriptyline, he or she should be aware of these side effects and a lower dose may be indicated. On the other hand, an increase in the dosage of a TCA may be required if verapamil is discontinued from the combination.

Action: Monitor for anticholinergic effects if verapamil is added to a patient previously stabilized on amitriptyline, imipramine, or nortriptyline adjust the dose (upward) if verapamil is discontinued from combination therapy. Consider an alternative antidepressant other than TCA.

Amphetamine, Dextroamphetamine/Monoamine Oxidase Inhibitors (MAOI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of MAOIs and psychostimulants, e.g., amphetamine may result in severe headache, hypertensive crisis, cardiac arrhythmias, chest pain, hyperpyrexia and death. If the symptoms are not recognized and correctly treated, death may result. This is secondary to the increased norepinephrine availability.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing an MAOI before initiating therapy with amphetamine. Wait at least 2 weeks after discontinuing amphetamine before initiating therapy with an MAOI.

Amphetamine, Dextroamphetamine/Phenothiazines

Significant level 1: Major

Advice to the Practitioner: Co-administration of phenothiazines and amphetamine may produce seizures. In addition, amphetamine inhibits the antipsychotic effects of chlorpromazine and chlorpromazine reverses the anorectic effect of amphetamine. This is because of the antagonistic action of each other.

Action: Concurrent use of a phenothiazine and amphetamine is not recommended.

Amphetamine, Dextroamphetamine/Tricyclic Antidepressants (TCAs)

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of TCAs and amphetamine, dextroamphetamine or pemoline may cause increased effects of amphetamine, e.g., elevation of blood pressure, arrhythmias and CNS stimulation. This interaction is because of the additive effects of these drugs on norepinephrine neurotransmission.

Action: Patients who are on TCAs and amphetamine like agents require careful monitoring for hypertension,

arrhythmias and CNS stimulation. Avoid this combination if another option is available.

Benztropine/Clozapine

Significance level 2: Moderate

Advice to the Practitioner: Benzotropine has anticholinergic effects. When used with clozapine, increased anticholinergic and CNS effects may occur. This interaction may be a concern in patients on high doses of these agents. In a patient on clozapine, increased anticholinergic effects should be expected when benztropine is added. No action is necessary if a patient is already maintained on the 2 agents. If clozapine is being added to benztropine, increased anticholinergic effects should be expected.

Action: Avoid routine use of benztropine with clozapine. Consider atypical antipsychotics with reduced incidence of extrapyramidal symptoms (EPS) if it is problematic. Combined use should be limited to patients with signs and symptoms of EPS.

Benztropine/Haloperidol

Significance level 2: Moderate

Advice to the Practitioner: Both haloperidol and benztropine have anticholinergic effects. The combination of haloperidol and other anticholinergic agents have resulted in worsening of schizophrenic symptoms and may increase the risk of tardive dyskinesias.

Action: Avoid routine use of benztropine with haloperidol. Consider atypical antipsychotics with reduced incidence of EPS if it is problematic. Combined use should be limited to patients with signs and symptoms of EPS.

Benztropine/Phenothiazines

Significance level 2: Moderate

Benzotropine has anticholinergic effects. When used with a phenothiazine antidepressant, especially those with high anticholinergic effects, increased anticholinergic and CNS effects may occur. This interaction may be a concern in patients on high doses of these agents. In a patient on a phenothiazine, increased anticholinergic effects should be expected when benztropine is added. No action is necessary if a patient is already maintained on the 2 agents. If a phenothiazine is being added to benztropine, increased anticholinergic effects should be expected. Additionally, oral absorption of the phenothiazine may be decreased. It is unknown if spacing the doses of these agents would diminish this effect, but it is unlikely to have an impact as direct interference with absorption is not postulated to be the mechanism.

Action: Avoid routine use of benztropine with phenothiazines. Consider atypical antipsychotics with reduced incidence of EPS if it is problematic. Combined use should be limited to patients with signs and symptoms of EPS.

Bupropion/Carbamazepine

Significant level 2: Moderate

Advice to the Practitioner: Carbamazepine can significantly decrease peak bupropion concentrations and area under the plasma concentration-time curve (AUC). Carbamazepine increases the hepatic metabolism of bupropion via CYP-450 3A4 isoenzyme. If a patient is on bupropion and carbamazepine is added, it may decrease the effectiveness of bupropion. If a patient is on carbamazepine, bupropion is added, no action is necessary, as the dose of carbamazepine should be determined by the clinical efficacy. If the patient is stabilized on this combination, no action is required.

Action: Patient should be monitored for clinical response to bupropion. If an interaction is suspected, adjust therapy as indicated.

Bupropion/Monoamine Oxidase Inhibitors

Significant level 1: Major

Advice to the Practitioner: Co-administration of an MAOI and bupropion may result in bupropion toxicity (seizures, agitation, psychotic changes). If the symptoms are not recognized and correctly treated, death can result. The mechanism of this interaction has not been delineated.

Action: Combination of buspirone and MAOI's is contraindicated. Wait at least 2 weeks after discontinuing isocarboxazid before initiating therapy with bupropion.

Bupropion/Phenobarbital

Significant level 2: Mild

Advice to the Practitioner: Phenobarbital enhances metabolism of bupropion, resulting in decreased concentrations. If a patient is stable on the combination, no change in therapy is necessary. If a patient is on phenobarbital and bupropion is added, no action is necessary as the dose of bupropion will be determined by clinical response. If a patient is on bupropion and phenobarbital is added, the dose of bupropion may need to be adjusted based on clinical efficacy or serum levels.

Action: Monitor bupropion efficacy when phenobarbital is added to bupropion as indicated above.

Buspirone/Selective Serotonin Reuptake Inhibitors (SSRI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of buspirone and an SSRI may cause serotonin syndrome, characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering and tremor. This is secondary to inhibition of buspirone serotonergic effects.

Action: The combination of an SSRI and buspirone should be avoided.

Buspirone/Monoamine Oxidase Inhibitors (MAOI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of an MAOI- and buspirone may result in hypertensive crisis, a hyperserotonergic state characterized by symptoms such as

flushing, headache and elevation of blood pressure. If the symptoms are not recognized and correctly treated, death can result. This probably is secondary to increased norepinephrine availability.

Action: Combination of buspirone and MAOI's is contraindicated. Wait at least 2 weeks after discontinuing an MAOI before initiating therapy with buspirone.

Buspirone/Verapamil

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of buspirone and verapamil has been shown to increase the area under the concentration-time curve (AUC) and the maximum concentration of buspirone. Increased buspirone effects such as sedation may be seen. This is secondary to the inhibition of the CYP450 3A4—mediated first-pass metabolism of buspirone. If a patient is on buspirone and verapamil is added, monitor for increased buspirone levels and the need to decrease the dose of buspirone. If a patient is on verapamil and buspirone is added, no action is necessary, as the dose of buspirone should be determined by clinical efficacy.

Action: Monitor patients receiving combination of buspirone and verapamil for the increased buspirone effects such as sedation. An alternative anxiolytic agent may be used.

Carbamazepine/Donepezil

Significance level 3: Minor

Advice to the Practitioner: Carbamazepine induces the metabolism of donepezil via induction of the cytochrome P450 3A4 and 2D6 isoenzymes. Interactions of this type may take some time to onset or dissipate. If a patient is on carbamazepine and donepezil is added, no intervention is required, as the dose of donepezil will be determined by clinical efficacy. If a patient is stabilized on the combination, no action is necessary. If a patient is on donepezil and carbamazepine is added, decreased donepezil activity may be seen, and increased doses may be needed.

Action: Patients should be monitored for clinical response to donepezil when carbamazepine is added. The dose of donepezil may need to be adjusted when carbamazepine is added to or removed from the regimen.

Carbamazepine/Haloperidol

Significance level 2: Moderate

Advice to the Practitioner: Carbamazepine induces the metabolism of haloperidol via the cytochrome P450 3A4 and 2D6 isoenzymes. Interactions of this type may take some time to onset or dissipate. If a patient is on carbamazepine and haloperidol is added, no intervention is required, as the dose of haloperidol will be determined by clinical efficacy. If a patient is stabilized on the combination, no action is necessary. If a patient is on haloperidol and carbamazepine is added, decreased haloperidol effectiveness may be seen, and increased doses may be needed.

Action: Patients should be monitored for clinical response to haloperidol when carbamazepine is added. The dose of haloperidol may need to be adjusted when carbamazepine is added to or removed from the regimen.

Carbamazepine/Lithium

Significance level 2: Moderate

Advice to the Practitioner: The combination of lithium and carbamazepine has resulted in neurotoxicity, even with therapeutic concentrations. Reported symptoms include: unsteady gait, truncal tremors, ataxia, horizontal nystagmus, hyperflexia, muscle fasciculations, confusion, drowsiness, weakness, lethargy, and coarse tremor. When used together, patients must be educated and closely monitored.

Action: Monitor patients for symptoms listed above if the combination is necessary.

Carbamazepine/Monoamine Oxidase Inhibitors (MAOIs)

Significance level 1: Major

Advice to the Practitioner: Use of carbamazepine with a MAOI is contraindicated by the manufacturer, with a recommendation that at least 14 days elapse between the discontinuation of the MAOI and introduction of carbamazepine. Concomitant use has resulted in increased blood pressure, hyperpyrexia, and seizures. However, in refractory cases use of a MAOI with carbamazepine may be employed with appropriate monitoring and patient education.

Action: Avoid combination whenever possible. At least 14 days should elapse after discontinuing a MAOI before carbamazepine is introduced. If the combination is essential, closely monitor patient for the signs and symptoms listed above.

Carbamazepine/Nefazodone

Significance level 2: Moderate

Advice to the Practitioner: This combination represents a complex interaction. Nefazodone inhibits the metabolism of carbamazepine via inhibition of the cytochrome P450 3A4 isoenzyme. However, carbamazepine induces the metabolism of nefazodone by cytochrome P450 3A4 induction and has been reported to significantly reduce the serum levels of nefazodone.

Action: Patients should be monitored for clinical response to both nefazodone and carbamazepine. It is difficult to predict the impact of this combination because of the competitive and divergent effect on the same enzyme system. Monitoring of serum carbamazepine levels is essential when nefazodone is added, discontinued, or dose adjusted.

Carbamazepine/Olanzapine

Significance level 2: Moderate

Advice to the Practitioner: Carbamazepine induces the metabolism of olanzapine via induction of the cytochrome P450 1A2 isoenzyme. Interactions of this type may take some time to onset or dissipate. If a patient is on carbamazepine and olanzapine is added, no intervention is required,

as the dose of olanzapine will be determined by clinical efficacy. If a patient is stabilized on the combination, no action is necessary. If a patient is on olanzapine and carbamazepine is added, decreased olanzapine activity may be seen, and increased doses may be required.

Action: Patients should be monitored for clinical response to olanzapine when carbamazepine is added. The dose of olanzapine may need to be adjusted when carbamazepine is added or removed from the regimen.

Carbamazepine/Phenobarbital

Significance level 2: Moderate

Advice to the Practitioner: Phenobarbital induces CYP450 3A4 that metabolizes carbamazepine. The increase in metabolism significantly reduces plasma concentrations of carbamazepine. If a patient is on a stabilized dose of both drugs, no action is necessary. When phenobarbital is added to carbamazepine monitor patients for increased seizure activity and increase the carbamazepine dose if necessary. However, phenobarbital levels are not affected by carbamazepine.

Action: Monitor for increased seizure activity and increase the dose of carbamazepine if necessary when phenobarbital is added to carbamazepine.

Carbamazepine/Risperidone

Significance level 2: Moderate

Advice to the Practitioner: Carbamazepine induces the metabolism of risperidone via induction of the cytochrome P450 2D6 and 3A4 isoenzyme. Risperidone serum levels will decrease when carbamazepine is added, and have been reported to double when carbamazepine was discontinued. Interactions of this type may take some time to onset or dissipate. If a patient is on carbamazepine and risperidone is added, no intervention is required, as the dose of risperidone will be determined by clinical efficacy. If a patient is stabilized on the combination, no action is necessary. If a patient is on risperidone and carbamazepine is added, decreased risperidone activity may be seen, and increased doses may be needed.

Action: Patients should be monitored for their clinical response to risperidone when carbamazepine is added. The dose of risperidone may need to be adjusted when carbamazepine is added or removed from the regimen.

Carbamazepine/Selective Serotonin Reuptake Inhibitors (SSRIs)

Significance level 2: Moderate

Advice to the Practitioner: Carbamazepine levels may be increased by the addition of fluoxetine, fluvoxamine, and sertraline. In addition, serum levels of citalopram may be decreased by carbamazepine since it is metabolized by the P450 3A4 isoenzyme, which is induced by carbamazepine. Paroxetine has not been reported to be affected by carbamazepine, and does not itself appear to affect carbamazepine.

Action: Monitor patient for symptoms of increased carbamazepine concentration and adjust doses as needed. If using citalopram, monitor patients for inadequate therapeutic efficacy and increase dosage if needed. Use of paroxetine may be considered.

Carbamazepine/Trazodone

Significance level 2: Moderate

Advice to the Practitioner: Trazodone inhibits the metabolism of carbamazepine via induction of the cytochrome P450 3A4 isoenzyme. Carbamazepine clearance may be decreased, resulting in carbamazepine toxicity. Also plasma levels of trazodone and its active metabolite may be decreased from enhanced metabolism. Interactions of this type may take some time to onset or dissipate. If a patient is on carbamazepine and trazodone is added, increased carbamazepine concentration and toxicity may be seen. If a patient is stabilized on the combination, no action is necessary. If a patient is on trazodone, and carbamazepine is added, no action is necessary as the dose of carbamazepine will be determined by serum levels and clinical efficacy.

Action: Carbamazepine serum levels should be monitored when trazodone is added to or removed from carbamazepine therapy. Patients should be monitored for clinical signs and symptoms of carbamazepine toxicity.

Carbamazepine/Tricyclic Antidepressants (TCA)

Significance level 2: Moderate

Advice to the Practitioner: Addition of carbamazepine to a TCA has been associated with a significant reduction in serum concentration of the TCA. Reductions have been reported with amitriptyline, nortriptyline, imipramine, and desipramine. It is believed to be a result of carbamazepine induced metabolism of TCAs. Interactions of this type may take some time to onset or dissipate. If a patient is on carbamazepine and TCA is added, no intervention is required, as the dose of TCA will be determined by clinical efficacy. If a patient is stabilized on the combination, no action is necessary. If a patient is on TCA and carbamazepine is added, decreased TCA activity may be seen, and increased doses may be needed.

Action: Monitor patient for symptoms of decreased TCA concentration and adjust dose as needed. Obtaining serum levels of the TCA may be helpful.

Carbamazepine/Verapamil

Significance level 2: Moderate

Advice to the Practitioner: Co-administration of carbamazepine and verapamil has resulted in increased carbamazepine levels and toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, and coma). The probable mechanism is decreased carbamazepine metabolism by verapamil. If the patient were stable on this combination, no action would be necessary. Decrease or increase in carbamazepine dose may be required when verapamil is administered or withdrawn, respectively.

Action: Reduction in the dose of carbamazepine may be required when verapamil is added, and increasing the dose of carbamazepine when verapamil is withdrawn may be necessary.

Clozapine/Benzodiazepines

Significance level 2: Moderate

Advice to the Practitioner: There have been reports of cardiorespiratory collapse when benzodiazepines have been used with clozapine. It is unclear what the mechanism of this reaction is and it has been rarely reported.

Action: Monitor patient when this combination is used.

Clozapine/Carbamazepine

Significance level 2: Moderate

Advice to the Practitioner: Both clozapine and carbamazepine are associated with agranulocytosis and bone marrow suppression. Additionally, carbamazepine is an enzyme inducer and may decrease clozapine serum levels. Interactions of this type may take some time to onset or dissipate. If a patient is maintained on the combination of carbamazepine with clozapine, no action is necessary. If a patient is on carbamazepine and clozapine is added, no action is necessary as the dose of clozapine will be determined by serum levels and clinical response. If a patient is on clozapine and carbamazepine is added, clozapine levels and toxicity should be monitored as the metabolism of clozapine will be increased and serum levels may decrease.

Action: Use this combination only if necessary, and then monitor complete blood counts (CBC) and clozapine levels as indicated above.

Clozapine/Lithium

Significance level 2: Moderate

Advice to the Practitioner: When lithium has been added to antipsychotic agents, encephalopathic symptoms have occurred. In addition, weakness, dyskinesia, and increased EPS, and brain damage have been reported. Some data suggest that lithium levels <0.5 mEq/L minimize this risk, however, this has not been fully established. This interaction is not commonly seen, and lithium is frequently added to many antipsychotic agents without any interaction.

Action: When using lithium and clozapine together, monitor patient for weakness, EPS, and encephalopathic symptoms.

Clozapine/Phenobarbital

Significance level 2: Moderate

Advice to the Practitioner: Phenobarbital is an enzyme inducer and may decrease clozapine serum levels. Interactions of this type may take some time to be observed or dissipate. If a patient is maintained on the combination of phenobarbital with clozapine, no action is necessary. If a patient is on phenobarbital and clozapine is added, no action is necessary as the dose of clozapine will be determined by serum levels and clinical response. If a patient is on clozapine and phenobarbital is added, clozapine levels should be

monitored as the metabolism of clozapine will be increased and serum levels may decrease with consequent diminished effectiveness.

Action: Monitor clozapine serum levels and response when adding or removing phenobarbital from a patient's medication regimen.

Clozapine/Selective Serotonin Reuptake Inhibitors (SSRIs)

Significance level 2: Moderate

Advice to the Practitioner: Clozapine is hepatically metabolized via the cytochrome P450 2D6 and 1A2 pathway. Fluoxetine and sertraline are inhibitors of the 2D6 enzyme and fluvoxamine inhibits the 1A2 enzyme, and they may increase clozapine levels resulting in toxicity when used in combination. Interactions of this type may take some time to occur or dissipate. If a patient is maintained on the combination of fluoxetine, sertraline or fluvoxamine, with clozapine, no action is necessary. If a patient is on fluoxetine, fluvoxamine or sertraline and clozapine is added, no action is necessary as the dose of clozapine will be determined by serum levels and the clinical response. If a patient is on clozapine and fluoxetine, fluvoxamine or sertraline is added, clozapine levels and toxicity should be monitored as the metabolism of clozapine will be decreased and serum levels may increase to toxic levels.

Action: Monitor patient and clozapine levels as above with dose adjustments made as required. Alternatively, paroxetine or citalopram may be used as they are less likely to impact the 2D6 or 1A2 enzymes.

Clozapine/Venlafaxine

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of venlafaxine and clozapine result in increased serum concentrations of both, which are associated with clozapine toxicity (e.g., dizziness, sedation, vomiting, hypotension) and venlafaxine toxicity (e.g., somnolence). This is because of the competitive inhibition of the metabolism of one another.

Action: Careful monitoring of signs of toxicity of both drugs is required.

Diazepam/Selective Serotonin Reuptake Inhibitors (Fluoxetine, Fluvoxamine, Sertraline)

Significance level 2: Moderate

Advice to the Practitioner: Fluoxetine, fluvoxamine, and sertraline inhibit cytochrome P450 3A4 that metabolizes diazepam. Interactions of this type may take some time to occur or dissipate. If a patient is on diazepam and one of these SSRI's are added, increased benzodiazepine activity may be seen. If a patient is stabilized on the combination, no action is necessary. If a patient is on any one the above named SSRI's and diazepam is added, no action is necessary, as the dose of diazepam will be determined by clinical efficacy.

Action: Monitor benzodiazepine efficacy and adjust dose as needed as indicated above. An unaffected ben-

zodiazepine or paroxetine may be considered as alternatives.

Diphenhydramine/Tricyclic Antidepressants (TCA)

Significance level 2: Moderate

Advice to the Practitioner: TCAs and diphenhydramine have anticholinergic effects. Use of both agents may result in adynamic ileus, urinary retention, or chronic glaucoma. This may be more problematic in the elderly or in patients sensitive to anticholinergic effects.

Action: In patients where additional anticholinergic effects are undesirable, or in elderly patients, use of a TCA with lower anticholinergic activity or an antidepressant of a different class is recommended.

Haloperidol/Clozapine, Olanzapine

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of haloperidol and olanzapine or clozapine may result in increased serum concentration of haloperidol which is associated with Parkinsonism symptoms (cogwheel rigidity, unstable gait). Haloperidol metabolism is inhibited by clozapine and olanzapine via CYT P45 2D6. If a patient is on a haloperidol and clozapine or olanzapine is added, monitor for increased haloperidol levels and the need to decrease the dose of haloperidol. If a patient is clozapine or olanzapine and a haloperidol is added, no action is necessary, as the dose of clozapine or olanzapine should be determined by clinical efficacy.

Action: Monitor for extrapyramidal symptoms when olanzapine or clozapine are added to haloperidol. Monitor and adjust the dose of haloperidol if necessary when starting or stopping clozapine or olanzapine.

Haloperidol/Fluvoxamine, Fluoxetine, Paroxetine, Nefazodone

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of haloperidol and fluoxetine, fluvoxamine or nefazodone result in increased serum concentration of haloperidol that is associated with extrapyramidal symptoms, akathisia, tongue stiffness and cognitive impairment. The SSRI's and nefazodone inhibit the metabolism of haloperidol and its clearance. If patient is on haloperidol and the above named SSRIs and nefazodone are added, increase haloperidol level will be seen. Decreased the dose of haloperidol. If a patient is on SSRIs or nefazodone and haloperidol is added, no action is necessary, as the dose of SSRI or nefazodone should be determined by the clinical efficacy.

Action: Monitor for signs of extrapyramidal symptoms and also cognitive impairment when using the above combination. When patients are stabilized on haloperidol, alter the dose when starting or stopping SSRI's or nefazodone.

Haloperidol/Phenothiazines

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of haloperidol and phenothiazines will result in increased serum concentration of haloperidol that is associated with the risk of toxicities. Haloperidol metabolism is inhibited by phenothiazine via CYT P45 2D6. If a patient is on haloperidol and phenothiazine is added, monitor for increased haloperidol levels and the dose of haloperidol needs to be decreased. If a patient is on a phenothiazine and haloperidol is added, no action is necessary, as the dose of phenothiazine should be determined by clinical efficacy.

Action: Monitor the clinical response of the patient to haloperidol when a phenothiazine is started or stopped.

Lamotrigine/Carbamazepine, Oxcarbamazepine

Significance level 2: Moderate

Advice to the Practitioner: Concurrent use of lamotrigine and carbamazepine can result in a 40% decrease in lamotrigine steady state levels and a doubling of lamotrigine clearance leading to a decreased pharmacologic effect of lamotrigine. Reduced lamotrigine efficacy can lead to the loss of seizure control and mood stabilization. The exact mechanism is not known, but it maybe because of carbamazepine's potent ability to induce CYP3A4 and other enzymes in the liver accelerating the metabolism of lamotrigine. Loss of seizure control is more likely to occur when the initial dose of carbamazepine is high and lamotrigine is added. Oxcarbamazepine has a less pronounced effect on lamotrigine levels, but the effect is still significant.

Action: Monitor for loss of efficacy. May need to consider increasing lamotrigine dose and/or decreasing the carbamazepine/oxcarbamazepine dose.

Lamotrigine/Phenobarbital

Significance level 2: Moderate

Advice to the Practitioner: The administration of phenobarbital significantly decreases the half-life of lamotrigine because of its ability to induce hepatic enzymes. If a patient is on lamotrigine and phenobarbital is added, an increase in lamotrigine dose may be necessary. If a patient is on the combination and phenobarbital is discontinued, the lamotrigine dose may need to be decreased. If a patient is on both drugs and well maintained, no action is necessary.

Action: Monitor for loss of seizure control and the need to increase or decrease the lamotrigine dose. When patients are receiving concurrent therapy and the phenobarbital dose is decreased or discontinued, monitor patients carefully for lamotrigine toxicity and the need to lower the lamotrigine dose.

Lamotrigine/Valproic Acid

Significance level 2: Moderate

Advice to the Practitioner: Concurrent use of lamotrigine and valproic acid can result in a 2-fold increase in the normal half life of lamotrigine with a significant rise in plasma concentrations. The mechanism of interaction is competitive inhibition between lamotrigine and valproic

acid for hepatic glucuronidation. In addition, use of valproic acid and lamotrigine may increase the risk of severe skin reactions such as Stevens-Johnson Syndrome. When adding lamotrigine to valproic acid, begin at a lower dose (25 mg qod). Target doses are also lower (100-200 mg daily). When adding valproic acid to lamotrigine, decreasing the lamotrigine dose by 50% has been recommended, and patients should be monitored for any signs of skin rash.

Action: Use of a lower dose of lamotrigine with valproic acid is recommended. Patients should contact their health care practitioner if a skin rash develops, and practitioners should be advised that the risk of severe skin reactions is increased with combination therapy.

Lithium/Antipsychotics

Significant level 2: Moderate

Advice to the Practitioner: When lithium has been added to antipsychotic agents, encephalopathic symptoms have occurred. In addition, weakness, dyskinesia and increased EPS, and brain damage have been reported. Some data suggest that lithium levels <0.5 mEq/L minimize this risk, however, this has not been fully established. This interaction is not commonly seen, and lithium is frequently added to many antipsychotic agents without any interaction. (See also **Phenothiazines/Lithium.**)

Action: When using lithium and clozapine together, monitor patient for weakness, EPS and encephalopathic symptoms.

Lithium/Monoamine Oxidase Inhibitors (MAOI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of an MAOI and lithium may result in neuroleptic malignant syndrome (incoherent speech, reduced consciousness, muscular rigidity, nystagmas, hyperreflexia, diaphoresis, shivering, and tremor). If the symptoms are not recognized and correctly treated, death can result. The mechanism is unknown.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing MAOI before initiating therapy with lithium.

Lithium/Tricyclic Antidepressants (TCA)

Significant level 2: Moderate

Advice to the Practitioner: The addition of lithium to patients who are taking TCAs may result in neurotoxicity (tremors, ataxia, and seizures) and worsening of the mania. The mechanism is not fully understood, but may be related to the synergistic interaction between lithium and TCAs (imipramine).

Action: Use this combination cautiously. Discontinue either lithium or the TCA if any interaction is suspected. Serum lithium levels should be monitored periodically and adjust the dose periodically. The clinician may prefer to use other antidepressants, e.g., SSRI's.

Lithium/Verapamil

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of lithium and verapamil may result in the decreased serum concentration of lithium that is associated with the worsening of mania. Neurotoxicity and bradycardia may occur when calcium channel blockers are combined with lithium. This interaction is because of the synergistic decrease of the transport of the calcium ion. If a patient is on lithium and verapamil is added, monitor for decreased lithium levels and the dose of lithium may need to be increased. If verapamil is taken away lithium dosage may need to be increased.

Action: Careful monitoring of lithium levels, signs of mania and symptoms of neurotoxicity, and bradycardia is indicated when verapamil is added or discontinued to lithium.

Loxapine/Lorazepam

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of lorazepam and loxapine may develop severe respiratory depression, stupor and hypotension. The mechanism of action is unknown. If a patient is stabilized on the combination, no action is necessary.

Action: Careful monitoring of patients receiving loxapine and lorazepam for excessive sedation and respiratory depression is required.

Nefazodone/Benzodiazepines

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of nefazodone and alprazolam or triazolam may result in increased plasma concentration of benzodiazepines that are associated with impaired psychomotor performance and memory. Nefazodone inhibits the metabolism of above benzodiazepines via CYP-450 3A4 isoenzyme. If a patient is stabilized on the combination, no action is necessary. If the patient is on alprazolam or triazolam and the nefazodone is added, increased benzodiazepines activity will be seen.

If a patient is on nefazodone and benzodiazepines is added, no action is necessary, as the dose of benzodiazepines should be determined by clinical efficacy.

Action: Monitor for signs of benzodiazepines efficacy and adjust dose as indicated above. Consider switching to an unaffected benzodiazepine or, paroxetine may be considered as alternatives.

Nefazodone/Monoamine Oxidase Inhibitors (MAOI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of MAOIs and nefazodone may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state. If the symptoms are not recognized and correctly treated, death may result. The mechanism is secondary to inhibition of serotonin metabolism by monoamine oxidase.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing MAOI before initiating therapy with nefazodone. Wait at least 2 weeks after discontinuing nefazodone before initiating therapy with MAOI's.

Nefazodone/Pimozide

Significant level 1: Major

Advice to the Practitioner: Nefazodone inhibits the metabolism of pimozide via the CYP-450 3A4 isoenzyme. Co-administration of nefazodone and pimozide result in increased plasma concentration of pimozide which have been associated with adverse cardiovascular effects including QT prolongation, cardiac arrhythmia, torsades de pointes, and sudden death.

Action: Because of potential for significant life threatening, proarrhythmic effects, concurrent administration of nefazodone and pimozide is contraindicated.

Nefazodone/Tricyclic Antidepressants (TCA)

Significant level 1: Major

Advice to the Practitioner: Co-administration of TCAs and nefazodone may result in serotonin syndrome, a hyper-serotonergic state. If the symptoms are not recognized and correctly treated, death may result. The mechanism is because of altered serotonin metabolism.

Action: Combination therapy should be avoided. Wait at least 2 weeks after discontinuing TCA's before initiating therapy with nefazodone. Wait at least 2 weeks after discontinuing nefazodone before initiating therapy with TCA's.

Olanzapine/Fluvoxamine

Significance level 2: Moderate

Advice to the Practitioner: Concurrent use of olanzapine and fluvoxamine may cause an increase in olanzapine levels. Fluvoxamine inhibits P450 1A2 isoenzyme that is partially responsible for olanzapine metabolism. Monitor for increased olanzapine adverse reactions (tachycardia, orthostatic hypertension, seizures). If a patient is on olanzapine and fluvoxamine is added, monitor for increased olanzapine levels and the need to decrease the dose of olanzapine. If a patient is stabilized on the combination, no action is necessary. If a patient is on the combination and fluvoxamine is discontinued, monitor for decreased olanzapine efficacy and adjust the dose as needed.

Action: Monitor for olanzapine efficacy and adjust dose as needed.

Oxazepam/Phenobarbital

Significance level 2: Moderate

Advice to the Practitioner: Concurrent use of oxazepam and phenobarbital results in a shortened elimination half-life and higher clearance of oxazepam. The mechanism of action is enhanced activity of glucuronyl transferase activity. If phenobarbital is added to oxazepam it may be necessary to increase the dose of oxazepam. If a patient is stabilized on the combination no action is necessary.

Action: Increased dosage of oxazepam may be needed if phenobarbital is added, or use an unaffected benzodiazepine.

Paroxetine/Nefazodone

Significance level 1: Major

Advice to the Practitioner: Co-administration of paroxetine and nefazodone may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. The mechanism is because of inhibition of serotonin reuptake.

Action: Combination of these 2 drugs should be avoided. Wait at least 7 days after discontinuing nefazodone before initiating therapy with paroxetine.

Phenobarbital/Clonazepam

Significance level 2: Moderate

Advice to the Practitioner: Concurrent use of phenobarbital and clonazepam decreases the steady state plasma concentration of clonazepam. If a patient is on a stabilized dose of both drugs, no action is necessary. When phenobarbital is added to clonazepam there may be a loss of efficacy and a dosage adjustment may be needed. If phenobarbital is withdrawn from the combination there may be an increase in clonazepam levels and side effects. Dose adjustment may be necessary. The addition of clonazepam to phenobarbital does not effect phenobarbital plasma concentrations.

Action: Monitor patients for decreased efficacy of clonazepam if phenobarbital is added and increased clonazepam levels if phenobarbital is withdrawn. Dosage adjustments may be necessary.

Phenobarbital/Haloperidol

Significance level 2: Moderate

Advice to the Practitioner: Phenobarbital induces enzyme stimulation that can significantly lower haloperidol blood levels. When phenobarbital is added to haloperidol, patients experience a decrease in plasma concentrations. When adding phenobarbital to haloperidol, patients should be monitored for decreased efficacy and lower plasma levels of haloperidol. The dose of haloperidol may need to be increased when phenobarbital is given. When patients receive concurrent therapy and the dose of phenobarbital is decreased or discontinued, monitor patients for increased haloperidol levels and the need for a decreased dose.

Action: Monitor patients for increased or decreased haloperidol levels depending upon the addition or discontinuation of phenobarbital.

Phenobarbital/Monoamine Oxidase Inhibitors (MAOI)

Significance level 2: Moderate

Advice to the Practitioner: MAOIs may inhibit the metabolism of phenobarbital resulting in a prolonged effect of phenobarbital. Hypotension, increased CNS and respiratory effects may be observed. When an MAOI is added to phenobarbital, consider the need to decrease the phenobarbital

dose. In patients receiving concurrent therapy, if the MAOI dose is lowered or discontinued, consider increasing the dose of phenobarbital.

Action: Monitor patients for increased or decreased phenobarbital levels depending on the addition or discontinuation of the MAOI.

Phenobarbital/Paroxetine

Significance level 3: Minor

Advice to the Practitioner: Phenobarbital induces hepatic isoenzymes that may decrease serum concentrations of paroxetine. If a patient is maintained on the combination of phenobarbital with paroxetine, no action is necessary. If phenobarbital is added to paroxetine, monitor the patient for decreased paroxetine efficacy and the need to increase the paroxetine dose.

Action: Monitor paroxetine efficacy and adjust the dose as indicated above.

Phenobarbital/Thioridazine

Significance level 2: Moderate

Advice to the Practitioner: Concomitant administration has resulted in reports of decreased effectiveness of both phenobarbital and thioridazine. In addition, phenobarbital may decrease thioridazine levels because of the induction of hepatic enzymes. Patients should be monitored for decreased therapeutic effects for one or both drugs when adding one to the other. If a patient is maintained on the combination no action is necessary, but if one drug is discontinued the patient should be monitored for increase levels and adverse reactions.

Action: Monitor patients for increased or decreased drug effects of both drugs when changing therapy or adding either agent.

Phenobarbital/Tricyclic Antidepressants (TCA)

Significance level 2: Moderate

Advice to the Practitioner: Tricyclic antidepressants have been reported to reduce seizure threshold resulting in possible loss of seizure control. When adding a TCA to phenobarbital, patients should be monitored closely for loss of seizure control. An increase in phenobarbital dose may be necessary. If a TCA is discontinued from combination therapy, monitor patients for increased phenobarbital adverse reactions and the need to decrease the dose of phenobarbital. In combination, additive CNS and respiratory depressant effects are also possible, resulting in the need to adjust the dose of one or both drugs. It has been reported that phenobarbital may stimulate the metabolism of TCA resulting in decreased serum levels of the TCA and their therapeutic effectiveness. When adding phenobarbital to a TCA, it may be necessary to increase the TCA dose to maintain therapeutic levels. If phenobarbital is discontinued from combination therapy, it may be necessary to decrease the TCA dose.

Action: Monitor patients for reduced seizure control, CNS and respiratory depressant effects, and changes in TCA levels and efficacy. Dosage adjustments may be necessary.

Phenobarbital/Valproic Acid

Significance level 2: moderate

Advice to the Practitioner: Concomitant administration of phenobarbital and valproic acid results in the inhibition of phenobarbital metabolism and increased serum levels of phenobarbital. Patients should be monitored for serum levels and signs of phenobarbital toxicity. When adding valproic acid to phenobarbital it may be necessary to decrease the phenobarbital dose. If a patient is on the combination and valproic acid is discontinued phenobarbital levels may decrease requiring a dose adjustment. Concurrent phenobarbital and valproic acid therapy shortens the serum half-life of valproate because of hepatic enzyme induction. This results in a 10% increase in valproic acid clearance.

Action: Monitor patients for changes in phenobarbital serum concentration when adding or discontinuing valproic acid. Concurrent use may also increase valproic acid clearance. Adjust doses accordingly.

Phenobarbital/Verapamil

Significance level 3: Minor

Advice to the Practitioner: Concurrent use of oral phenobarbital resulted in a significant decrease in the concentration of verapamil. A possible mechanism is the increase in first pass hepatic metabolism of verapamil by phenobarbital. If phenobarbital is added to verapamil, the amounts of the latter may need to be increased to maintain an optimum effect; and, a higher dose of verapamil may be required when it is added to a patient currently taking phenobarbital.

Action: An increase of dose of verapamil may be required in a previously stabilized patient when phenobarbital is added; the verapamil dose should be adjusted (decreased) when phenobarbital is withdrawn from the combination.

Phenothiazines/Lithium

Significant level 2: Moderate

Advice to the Practitioner: When lithium has been added to antipsychotic agents, encephalopathic symptoms have occurred. In addition, weakness, dyskinesia and increased EPS, and brain damage have been reported. Some data suggest that lithium levels <0.5 mEq/L minimize this risk, however, this has not been fully established. This interaction is not commonly seen, and lithium is frequently added to many antipsychotic agents without any interaction.

Action: When using lithium and a phenothiazine together, monitor patient for weakness, EPS, and encephalopathic symptoms.

Phenothiazines/Pimozide

Significant level 1: Major

Advice to the Practitioner: Combination of a phenothiazine and pimozide is associated with adverse cardiovascular effects including QT prolongation, cardiac arrhythmia, torsades de pointes, and sudden death. This can be secondary to possible additive prolongation of the QTc interval.

Action: The concurrent administration of a phenothiazine and pimozide is contraindicated.

Phenothiazines/Propranolol

Significant level 1: Major

Advice to the Practitioner: Co-administration of propranolol and a phenothiazine may cause increased risk of phenothiazine toxicity, e.g., QT prolongation, torsades de pointes, cardiac arrest. The mechanism of action is a result of the inhibition of phenothiazine metabolism via CYP450 2D6 isoenzyme.

Action: Concurrent administration of phenothiazines and propranolol is contraindicated because of potential life-threatening cardiac arrhythmias.

Phenothiazines/Selective Serotonin Reuptake Inhibitors (SSRI)

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of phenothiazines and SSRIs results in increased phenothiazines plasma levels which may cause adverse effects, e.g., excessive sedation, extrapyramidal symptoms, impaired psychomotor performance and memory. This is secondary to the decreased metabolism of the phenothiazines via the inhibition of CYP450 2D6 isoenzyme. Not all SSRIs inhibit CYP 2D6 to the same extent. If a patient is on a phenothiazine and an SSRI is added, monitor for increased phenothiazine levels and the need to decrease the dose of phenothiazine. If a patient is on an SSRI and a phenothiazine is added, no action is necessary, as the dose of the phenothiazine will be determined by clinical efficacy.

Action: Carefully observe the clinical response when an SSRI is used in combination with a phenothiazine as indicated above.

Phenothiazines/Tricyclic Antidepressants (TCA)

Significant level 2: Mild

Advice to the Practitioner: Co-administration of phenothiazines and TCAs may result in an increase in anticholinergic effects (dry mouth, urinary retention, sedation).

Action: Careful monitoring of potential side effects is required for patients receiving phenothiazines and TCAs

Pimozide/Tricyclic Antidepressants (TCA)

Significant level 1: Major

Advice to the Practitioner: The concurrent administration of pimozide and tricyclic antidepressants results in the increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrests). This is secondary to the additive effects on QT interval.

Action: Concurrent administration of TCA and pimozide is contraindicated.

Quetiapine/Barbiturate

Significant level 3: Minor

Advice to the Practitioner: Co-administration of quetiapine and barbiturate may result in decreased quetiapine

serum concentrations. The mechanism of this drug interaction is unknown. If a patient is on the combination and stable, no action is required. Caution should be used when adding barbiturate as quetiapine efficacy can be decreased. When adding quetiapine to barbiturate monitor for the clinical effects of quetiapine.

Action: When co-administering quetiapine and barbiturate, monitor patients for quetiapine efficacy. An increase in quetiapine dose may be necessary.

Quetiapine/Carbamazepine

Significant level 3: Minor

Advice to the Practitioner: Co-administration of quetiapine and carbamazepine may result in decreased quetiapine serum concentrations. The mechanism of this drug interaction is unknown. If a patient is on the combination and stable, no action is required. Caution should be used when adding carbamazepine as quetiapine efficacy can be decreased. When adding quetiapine to carbamazepine monitor for the clinical effects of quetiapine.

Action: When co-administering quetiapine and carbamazepine, monitor patients for quetiapine efficacy. An increase in quetiapine dose may be necessary.

Quetiapine/Lorazepam

Significance level 3: Minor

Advice to the Practitioner: Co-administration of quetiapine and lorazepam decreased the mean oral clearance of lorazepam resulting in increased lorazepam serum concentrations. The mechanism of this drug interaction is unknown. Caution should be used when adding quetiapine to lorazepam. If a patient is on the combination and stable, no action is required. When adding lorazepam to quetiapine monitor for the clinical efficacy of lorazepam.

Action: When co-administering quetiapine and lorazepam, monitor patients for excessive lorazepam adverse effects including sedation, dizziness, and ataxia.

Quetiapine/Thioridazine

Significance level 2: Moderate

Advice to the Practitioner: Co-administration of quetiapine and thioridazine increased the oral clearance of quetiapine resulting in decreased quetiapine serum concentrations, which is associated with its decreased effectiveness. The mechanism of this drug interaction is unknown. If a patient is on the combination and stable, no action is required. Caution should be used when adding thioridazine as quetiapine efficacy can be decreased. When adding quetiapine to thioridazine monitor for the clinical affects of quetiapine.

Action: When co-administering quetiapine and thioridazine, monitor patients for quetiapine efficacy. An increase in quetiapine dose may be necessary.

Risperidone/Selective Serotonin Reuptake Inhibitors (SSRI)

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of risperidone and an SSRI may result in serotonin syndrome (hypertension, hyperthermia, myoclonus, mental changes). The mechanism of this drug interaction is unknown. Clinicians should be aware of the increased risk of serotonin syndrome in patients receiving potent serotonergic agents.

Action: When co-administering an SSRI and risperidone, monitor patients for excessive adverse effects like serotonin toxicity. Alternative agents should be employed if possible.

Risperidone/SSRIs—Fluvoxamine, Fluoxetine

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of risperidone and fluvoxamine or fluoxetine may increase serum concentrations of risperidone. Fluvoxamine and fluoxetine inhibit cytochrome P450 2D6 and 3A4, isoenzymes partially responsible for risperidone metabolism. This may result in risperidone toxicity.

Action: Concurrent administration of risperidone and fluvoxamine or fluoxetine should be avoided.

Selegiline/Monoamine Oxidase-A Inhibitors (MAO-AI)

Significance level 1: Major

Advice to the Practitioner: Concurrent use of selegiline (a selective MAO-B inhibitor) and a monoamine oxidase-A inhibitor antidepressant is potentially hazardous and may result in synergistic pharmacologic effects leading to excessive monoamine oxidase inhibition causing hypertensive crisis, fever, marked sweating, tremor, excitation, seizures, delirium, coma and circulatory collapse. **This is particularly more likely to occur if the dose of selegiline exceeds 10 mg daily, above which dose the drug can inhibit the MAO-A enzyme and acts as a nonselective MAO inhibitor.** If the patient is stable on the combination, no action is needed. Caution should be used, however, when adding selegiline to an MAO-AI or an MAO-AI to selegiline as both drugs potentiate inhibition of monoamine oxidase.

Action: Closely monitor patients for adverse effects of synergistic monoamine oxidase inhibition if concurrent use is necessary. Severe adverse interactions may occur (hypertensive crisis, fever, marked sweating, tremor, excitation, seizures, delirium, coma, and circulatory collapse).

Selegiline/Selective Serotonin Reuptake Inhibitors (SSRI), nefazodone, venlafaxine, buspirone

Significance level 1: Major

Advice to the Practitioner: Concurrent use of selegiline (a selective MAO-B inhibitor) and an SSRI or a serotonin affinity antidepressant is potentially hazardous and may result in synergistic pharmacologic effects leading to excessive serotonergic stimulation causing serotonin syndrome (hypertension, hyperthermia, myoclonus and mental status changes). **This is particularly more likely to**

occur if the dose of selegiline exceeds 10 mg daily, above which dose the drug can inhibit the MAO-A enzyme and acts as a nonselective MAO inhibitor. If the patient is stable on the combination, no action is needed. Caution should be used, however, when adding selegiline to an SSRI or an SSRI to selegiline as both drugs potentiate serotonin effects.

Action: Closely monitor patients for adverse serotonergic effects if concurrent use is necessary. Severe interactions—the serotonin syndrome could occur (hypertension, hyperthermia, myoclonus, and mental status changes).

Selegiline/Tricyclic Antidepressants (TCA)

Significance level 1: Major

Advice to the Practitioner: Concurrent use of selegiline (a selective MAO-B inhibitor) and a TCA antidepressant is potentially hazardous and may result in synergistic pharmacologic effects leading to excessive serotonergic stimulation causing the serotonin syndrome (hypertension, hyperthermia, myoclonus and mental status changes). **This is particularly more likely to occur if the dose of selegiline exceeds 10 mg daily, above which dose the drug can inhibit the MAO-A enzyme and acts as a nonselective MAO inhibitor.** If the patient is stable on the combination, no action is needed. Caution should be used, however, when adding selegiline to a TCA or TCA to selegiline as both drugs potentiate serotonin effects.

Action: Closely monitor patients for adverse serotonergic effects if concurrent use is necessary. Severe interactions—the serotonin syndrome could occur (hypertension, hyperthermia, myoclonus, and mental status changes).

Selective Serotonin Reuptake Inhibitors (SSRI)/Lithium

Significance level 1: Major

Advice to the Practitioner: Concurrent use of lithium and SSRIs may increase lithium levels and cause neurotoxicity, serotonin syndrome, somnolence, and mania. The exact mechanism is not known. Caution should be taken when using this combination. If a patient is stabilized on the combination, no action is necessary.

Action: Monitor signs of lithium toxicity with concomitant therapy; dosage adjustment may be necessary. Serum lithium levels should also be considered with the addition of an SSRI and periodically throughout therapy to assure stability.

Selective Serotonin Reuptake Inhibitors (SSRI)/Monoamine oxidase inhibitors (MAOI)

Significance level 1: Major

Advice to the Practitioner: Co-administration of an MAOI and an SSRI may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the symptoms are not recognized and correctly treated,

death may result. The mechanism is because of inhibition of serotonin metabolism by monoamine oxidase.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing MAOI before initiating therapy with SSRIs. Wait at least 2 weeks after discontinuing SSRIs before initiating therapy with MAOI.

Selective Serotonin Reuptake Inhibitors (SSRI)/Propranolol

Significance level 2: Moderate

Advice to the Practitioner: Co-administration of propranolol and some SSRIs (fluoxetine, fluvoxamine, sertraline) may significantly increase serum concentration of propranolol levels. This is because of their inhibition of propranolol metabolism via CYP2D6. Elevated propranolol serum concentrations may be associated with an increased risk of bradycardia and hypotension, and chest pain. If a patient is on propranolol and a SSRI is added, monitor for increased propranolol levels and the need to decrease the dose of propranolol. If a patient is on any one of the above named SSRI's and a propranolol is added, no action is necessary, as the dose of benzodiazepines should be determined by clinical efficacy.

Action: Carefully monitor heart rate and blood pressure. The propranolol dose may need to be reduced if bradycardia or hypotension develop. Alternatively, use of atenolol, a β -blocker which does not undergo hepatic metabolism may be considered.

Tacrine/Fluvoxamine

Significance level 3: Minor

Advice to the Practitioner: Two studies involving healthy volunteers and using a single dose of tacrine found that fluvoxamine inhibited the metabolism of tacrine causing an increase in its plasma concentration and 3 of its metabolites. The probable mechanism is inhibition of CYP 1A2 isoenzymes by fluvoxamine.

Action: Although the exact clinical implications of this drug interaction are uncertain, patients receiving concurrent tacrine and fluvoxamine should be monitored for excessive tacrine adverse effects (including cholinergic effects) and liver function tests monitored for hepatotoxicity.

Tacrine/Haloperidol

Significance level 3: Minor

Advice to the Practitioner: Concurrent use of tacrine and haloperidol has resulted in Parkinsonian syndrome in 2 separate case reports. The mechanism is thought to be a synergistic effect of these drugs resulting in an increase in acetylcholine activity in the striatal region of the brain. The adverse effects of akinesia, shuffling gait, masked facies, slurred speech, lead-pipe rigidity, and/or cogwheel signs are thought to be caused by this increase in acetylcholine activity. If patients are on the combination and stable, no action is necessary. As both drugs increase acetylcholine

activity in the striatal region caution should be used when adding either drug to the other.

Action: Monitor patients closely for the signs and symptoms of Parkinsonian syndrome when adding either tacrine to haloperidol or haloperidol to tacrine.

Trazodone/Barbiturate and other sedatives

Significant level 3: Minor

Advice to the Practitioner: Co-administration of trazodone and sedatives resulting in sedative potentiation. The mechanism of this drug interaction is unknown. If a patient is on the combination and stable, no action is required. Caution should be used when adding barbiturates to trazodone.

Action: The dose of barbiturates should be reduced when co-administered with trazodone.

Trazodone/Haloperidol

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of trazodone and haloperidol may result in an increase level of the active metabolite of trazodone, m-chlorophenylpiperazine (m-CPP). The interaction is a result of the inhibition of CYP450 2D6 metabolism of m-CPP by haloperidol. If patient is on trazodone and haloperidol is added the dosage of the former may be decreased. If haloperidol is discontinued, the latter's dosage may need to be increased. The addition of trazodone to haloperidol does not change its plasma concentration.

Action: Careful monitoring of m-CPP level is suggested.

Trazodone/Selective Serotonin Reuptake Inhibitors (SSRI)

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of trazodone and an SSRI may increase the plasma concentration of trazodone. The mechanism of this drug interaction is possibly because of inhibition of the hepatic metabolism of trazodone. There is also a possibility of serotonin syndrome. Trazodone probably should be used with caution in patients receiving any SSRI or other serotonergic agent.

Action: Trazodone plasma levels should be monitored when it is added to an SSRI. Patients should be monitored for clinical signs and symptoms of serotonin syndrome.

Tricyclic Antidepressants (TCA)/Bupropion

Significant level 2: Moderate

Advice to the Practitioner: Bupropion causes increase plasma concentration of TCAs, producing an increase in pharmacologic and adverse effects. This is because of the inhibition of TCA metabolism by bupropion via CYT P450 2D6 isoenzyme. If a patient is on TCA and bupropion is added, serum concentrations of the TCA may be increased. If a patient is on bupropion and a TCA is added, no action is necessary, as the dose of TCAs should be determined by

the clinical efficacy. If the patient is stabilized on this combination, no action is required.

Action: Patient should be observed for clinical response of TCAs when bupropion therapy is started or stopped.

Tricyclic Antidepressants (TCA)/Monoamine Oxidase Inhibitors (MAOI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of MAOI and TCAs may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the symptoms are not recognized and correctly treated, death may result. The mechanism is from altered catecholamine uptake and metabolism.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing an MAOI before initiating therapy with TCA's. Wait at least 2 weeks after discontinuing TCA's before initiating therapy with an MAOI.

Tricyclic Antidepressants (TCA)/Selective Serotonin Reuptake Inhibitors (SSRI)

Significance level 2: Moderate

Advice to the Practitioner: Concurrent use of a TCA and SSRI can significantly increase the plasma levels of the TCA. Elevated nortriptyline levels can lead to increased signs of nortriptyline toxicity (urinary retention, dry mouth, sedation). Most SSRIs are inhibitors of the cytochrome P450 2D6 leading to increased nortriptyline levels. Fluoxetine and paroxetine are potent inhibitors of P450 2D6, sertraline to a lesser degree. When a SSRI inhibitor that significantly inhibits 2D6 is added to a TCA, monitor for TCA toxicity and the need to decrease the TCA dose. When administered together and the SSRI is discontinued, monitor for decreased plasma TCA levels and the need to increase the TCA dose. Plasma concentrations of the TCA should be monitored. No action is necessary, if the patient is already maintained successfully on the 2 drugs.

Action: Monitor tricyclic blood levels, for signs of TCA toxicity or decreased TCA efficacy when adding or discontinuing a SSRI regimen. Consider a dosage adjustment.

Valproic acid/Benzodiazepines (Diazepam, Lorazepam)

Significant level 3: Minor

Advice to the Practitioner: Co-administration of valproic acid and diazepam or lorazepam may result in increased benzodiazepine effects. It is thought that metabolism of lorazepam is inhibited by valproic acid, and that diazepam is displaced from its protein binding sites by valproic acid. If a patient is on valproic acid and lorazepam or diazepam are added, there is no need to alter therapy as the dose of the benzodiazepine will be determined by clinical response. If a

patient is on lorazepam or diazepam and valproic acid is added, the dose of the benzodiazepine may need to be reduced.

Action: Monitor for signs of excessive sedation when added valproic acid to lorazepam or diazepam. Use of an alternative benzodiazepine may also be considered.

Valproic Acid (VPA)/Carbamazepine

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of carbamazepine (CBZ) and VPA will increase the clearance of valproic acid and decrease VPA levels. Valproic acid may increase the concentration of the active metabolite of CBZ, which may result in toxicity, e.g., ataxia, nystagmus, diplopia, headache, seizure, coma. In addition, valproic acid displaces carbamazepine from its protein binding site. If a patient is on carbamazepine and valproic acid is added, monitor for increased levels of the active metabolite of carbamazepine and for signs and symptoms of toxicity. If a patient is on valproic acid and carbamazepine is added, monitor valproic acid levels and increase the dose of valproic acid as needed.

Action: Carefully monitor both valproic acid and carbamazepine serum concentrations when using the combination.

Venlafaxine/Bupropion

Significant level 3: Minor

Advice to the Practitioner: Co-administration of bupropion and venlafaxine may result in increased venlafaxine levels.

Action: Patients receiving venlafaxine and bupropion should be monitored for venlafaxine toxicities.

Venlafaxine/Monoamine Oxidase Inhibitors (MAOI)

Significant level 1: Major

Advice to the Practitioner: Co-administration of MAOI and venlafaxine may result in CNS toxicity or serotonin syndrome, a hyperserotonergic state characterized by symptoms such as restlessness, myoclonus, changes in mental status, hyperreflexia, diaphoresis, shivering, and tremor. If the symptoms are not recognized and correctly treated, death may result. The mechanism is from the inhibition of serotonin metabolism by monoamine oxidase.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing an MAOI before initiating therapy with venlafaxine. Wait at least 2 weeks after discontinuing venlafaxine before initiating therapy with an MAOI.

Venlafaxine/Selective Serotonin Reuptake Inhibitors (SSRIs)

Significant level 1: Major

Advice to the Practitioner: Co-administration of an SSRI and venlafaxine may result in CNS toxicity or serotonin syndrome. If the symptoms are not recognized and correctly treated, death may result. The mechanism is from altered serotonin metabolism.

Action: Combination of these 2 drugs should be avoided. Wait at least 2 weeks after discontinuing a SSRI before initiating therapy with venlafaxine. Wait at least 2 weeks after discontinuing venlafaxine before initiating therapy with a SSRI.

Venlafaxine/Phenobarbital

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of venlafaxine and phenobarbital may result in the decreased venlafaxine serum concentrations and thereby may reduce its efficacy. The mechanism is from the phenobarbital's enhancing metabolism of venlafaxine via CYT P450 2D6 isoenzyme.

Action: Careful monitoring of venlafaxine efficacy should be measured when this combination is used. Dose adjustment is necessary when Phenobarbital is added to or withdrawn from the combination.

Venlafaxine/Phenothiazines

Significant level 2: Moderate

Advice to the Practitioner: Co-administration of a phenothiazine and venlafaxine may cause neuroleptic malignant syndrome (profuse sweating, anxiety, tremor, rigidity, and hypertension). This is because of dopamine-inhibition effect of venlafaxine that augments dopamine-receptor inhibition by phenothiazines.

Action: Monitor patients receiving venlafaxine and a phenothiazine regarding neuroleptic malignant syndrome, which can be manifested as profuse sweating, increased heart rate, tremor, rigidity, and increased blood pressure.

Venlafaxine/Tricyclic Antidepressants (TCA)

Significant level 1: Major

Advice to the Practitioner: Co-administration of a TCA and venlafaxine may precipitate the serotonin syndrome and may cause increase concentration of both amitriptyline and venlafaxine. Venlafaxine is a weak inhibitor of CYP2D6, in addition to being metabolized by this enzyme and TCA is metabolized by CYP2D6 isoenzyme as well. Both agents competitively inhibit the metabolism of each others and both are serotonergic.

Action: Monitor patients receiving concurrent TCAs and venlafaxine for signs of TCA toxicity and venlafaxine toxicity. Doses of either or both drugs may need to be reduced.

Verapamil/ β -blockers

Significant level 2: Moderate

Advice to the Practitioner: β -blockers and verapamil have negative inotropic effects, slow AV conduction, and potentiate hypotension, bradycardia, congestive heart failure, and conduction abnormalities. This is secondary to decreased metabolism of beta blockers that results in deleterious cardiac effects. These agents are used together frequently for the management of hypertension.

Action: Combination of verapamil and beta blockers should be done cautiously.

Ziprasidone/Pimozide

Significant level 1: Major

Advice to the Practitioner: Combination of ziprasidone and pimozide have been associated with adverse cardiovascular effects including QT prolongation, cardiac arrhythmia, torsades de pointes, and sudden death. This can be secondary to possible additive prolongation of the QTc interval.

Action: Concurrent administration of ziprasidone and pimozide is contraindicated.

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