Drug Interactions

Cardiac and Respiratory Systems

Commonly prescribed cardiac drugs

- Adenosine
- Amiloride
- Amiodarone
- Amlodipine
- Aspirin
- Atenolol
- Atorvastatin
- Atropine
- Benazepril
- Bisoprolol
- Bretylium
- Bumetanide
- Candesartan
- Captopril
- Carvedilol
- Cerivastatin
- Cholestyramine
- Clonidine
- Clopidogrel
- Colestipol
- Digoxin
- Diltiazen
- Disopyramide
- Enalapril
- Eporostenol
- Felodipine
- Flecainide
- Fluvastatin
- Furosemide
- Gemfibrozil
- Heparin
- Hydralazine
- Hydrochlorothiazide
- Ibutilid

- Isosorbide
- dinitrate
- Labetalol
- Lidocaine
- Lisinopril
- Losartan
- Lovastatin
- Metolazone
- Metoprolol
- Mexiletine
- Minoxidil
- Nadolol
- Nicardipine
- Nifedipine
- Nimodipine
- Nitroglycerin
- Norepinephrine
- Phenylephrine
- Pravastatin
- Prazosin
- Procainamide
- Propafenone
- Propranolol
- Quinidine
- Simvastatin
- Sotalol
- Spironolactone
- Terazosin
- Ticlopidine
- Tocainide
- Torsemide
- Triamterene
- Verapamil
- Warfarin

Commonly prescribed psychotropic medications

- Amphetamine Benztropine Buproprion Carbamazepine Chlordiazepoxide Chlorpromazine Citalopram Clomipramine Clonazepam Clozapine Diazepam Diphenhydramine Divalproex sodium Fluoxetine Fluphenazine Fluvoxamine Gabapentin Haloperidol Imipramine Lamotrigine Lithium

- Lorazepam Methylphenidate Mirtazapine Nefazadone Nortriptyline Olanzapine Oxazepam Paroxetine Perphenazine Quetiapine Risperidone Sertindole Sertraline Thioridazine Thiothixene Tradozone Trifluoperazine Trihexiphenidyl Valproic acid Venlafaxine Zolpidem

SSRI’s

Quinidine/SSRI
Significance level 1: Major Advice to Practitioner

- Fluoxetine and paroxetine have greater inhibitory effect on CYP2D6 whereas fluvoxamine exerts a stronger inhibitory effect on CYP1A2 and CYP3A4.
- Overall enzyme studies reflect that fluvoxamine, fluoxetine, and sertraline inhibit the enzyme CYP3A4 and may decrease the metabolism of quinidine which then can result in quinidine toxicity (arrhythmia).
- On the other hand, quinidine inhibits the metabolism of fluvoxamine, paroxetine, and venlafaxine by inhibiting the enzyme CYP2D6 and thereby can increase their side effects.

Action:

- Monitoring the patient for quinidine and SSRI toxicity and follow higher blood levels.

Furosemide/Fluoxetine
Significance level 1: Major Advice to Practitioner:

- Furosemide and ACE inhibitors may contribute to the hyponatremia.
- Action: Monitor for hyponatremia in patients receiving both furosemide and fluoxetine.
- If hyponatremia develops, furosemide or fluoxetine dose should be discontinued or dose decreased.

Beta Blockers (Lipophilic Hepatically Metabolized)/Selective Serotonin Reuptake Inhibitors (Fluoxetine, Sertraline, Fluvoxamine, Paroxetine) Significance level 2: Moderate Advice to Practitioner:

- The combination of a selective serotonin reuptake inhibitor (SSRI: fluoxetine, sertraline, fluvoxamine, paroxetine) and a beta blocker (propranolol, metoprolol, labetalol) may result in an increase in the beta adrenergic blocking effect and cardiac toxicity.

- The mechanism is thought to involve inhibition of oxidative metabolism of the beta blocker by the SSRI (particularly P450 2D6 by fluoxetine and its metabolite norfluoxetine) and its interaction with 5-HT receptors in the atrium of the heart.

- Fluvoxamine and sertraline appear to be less potent P450 2D6 inhibitors.

- Likewise, the use of a water soluble, renally cleared beta blocker (sotalol, atenolol) is not subject to this interaction.

- If a patient has been stabilized on the combination, there is little need to alter therapy.

- When adding one drug to the other, patient's blood pressure and heart rate should be monitored and electrocardiograms should be obtained to monitor for dysrhythmias.

- Action:
- Monitor blood pressure and heart rate frequently when combining these drugs. Obtain serial ECGs to monitor for dysrhythmias and discontinue the combination if a dysrhythmia develops.

Flecainide/SSRIs
Significance level 2: Moderate Advice to Practitioner

- Flecainide is metabolized by cytochrome P450 2D6 enzyme which is found to be inhibited by fluoxetine, paroxetine, sertraline and if they are administered concomitantly, flecainide level may be raised higher than the expected level.

- Action: When co-administered, doses may need to be reduced. Monitoring heart rate and serial ECG can be advised as a precaution.

Warfarin/Fluvoxamine, Fluoxetine, Sertraline Significance level 2: Moderate Advice to Practitioner:

These SSRIs may decrease the metabolism of warfarin via the CYP 2C9, resulting in increased warfarin activity.

Action:

- Monitor PT or INR as indicated

Salicyclates/Fluoxetine Significance level 3: Minor Advice to Practitioner:

- Aspirin may result in the reappearance of hives initially caused by fluoxetine.
- The mechanism for this allergic reaction is unknown and can be moderately severe.
- Action: Be aware of potential reactions

Others

Clarithromycin/Erythromycin:

- Case of delirium with fluoxetine and case of serotonin syndrome with citalopram has been reported.

Linezolide

- Linezolid inhibits MAO
- Monitor for serotonergic effect

Diphenhydramine

- Increased plasma level of fluoxetine and paroxetine due to inhibited metabolism via CYP2D6

Corticosteroid

- Increased risk of GI bleeding

Theophylline

- Increased level of theophylline via fluvoxamine due to decreased metabolism via CYP1A2

TCA’s

Quinidine/TCA Significance level 1:
Major Advice to Practitioner:

- Both quinidine and TCA cause prolongation of Q-T interval, so concomitant use of these drugs could result in a fatal arrhythmia.
- Quinidine increases the blood level of TCA by inhibiting the enzyme cytochrome P450 2D which is responsible for the metabolism of TCAs.
- Imipramine clearance can be reduced by 35% and desipramine by 85% if it is administered concurrently with quinidine.
- It usually requires about 2 weeks to demonstrate clinically evident TCA side effects, but in the case of nortriptyline it may occur after a single dose of 50 mg of quinidine.

Action:

- Combination of these drugs should be avoided unless there is no alternative.

- If used in combination, cardiac effects should be monitored by serial ECG (approximately every month for 3 months or so) and TCA side effects (dry mouth, sedation, urinary retention) should also be monitored. Dose of the drugs should be titrated accordingly

Ibutilide/Tricyclic antidepressants Significance level 1: Major Advice to Practitioner:

Ibutilide increases the QT interval, and use with other agents that increase the QT interval is not recommended.

- Use of alternative antiarrhythmic agents should be considered when a patient presents with a history of therapeutic or possible excessive use of a tricyclic antidepressant or phenothiazine.

Action: Avoid the combination if possible.

Sympathomimetics/Tricyclic Antidepressants Significance level 1: Major Advice to Practitioner:

- Tricyclic antidepressants can potentiate the pressor effects of direct acting sympathomimetics such as dobutamine, norepinephrine, epinephrine, and phenylephrine and may decrease the pressor response to indirect-acting sympathomimetics such as dopamine.

- When these agents are administered concomitantly, close monitoring of blood pressure and heart rhythm is required.

- However, patients receiving these sympathomimetics normally receive close monitoring and careful dosage titration based on response as part of their treatment, and additional monitoring will not be needed.
- For a patient located outside of an ICU setting, additional monitoring should be employed.
- Action: Anticipate enhanced pressor effects with this combination

ACE Inhibitors (Enalapril)/Tricyclic Antidepressants (Clomipramine)

Significance level 2: Moderate Advice to Practitioner:

- The addition of clomipramine to long-standing enalapril therapy results in an increase of serum clomipramine with signs of toxicity developing (confusion, insomnia, irritability, and mood changes).
- If a patient is stabilized on the combination, there is little need to alter therapy.
- However, when one drug is added to the other, serum clomipramine levels should be monitored and the dosage of the clomipramine adjusted accordingly.

- Patients should be cautioned about the potential for toxicity and its signs and symptoms.

Action: Monitor clomipramine concentrations when using enalapril and clomipramine in combination.

Warfarin/Tricyclic Antidepressants Significance level 2: Moderate Advice to Practitioner:

- Use of some tricyclic antidepressants has been associated with increases in PT and increased bleeding.
- The mechanism of this interaction is unclear: reduced absorption and decreased metabolism have been suggested.
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- When a TCA is added to a previously stable regimen of warfarin, warfarin activity may be decreased.

- When warfarin is added to a regimen containing a TCA, no intervention would be required, as the dose of warfarin would be determined by prothrombin times or international normalized ratios.

Action: Monitor PT when adding a tricyclic antidepressant as recommended above.

Propafenone/Tricyclic Antidepressants Significance level 2: Moderate Advice to Practitioner:

- Propafenone inhibits cytochrome P450-2D6 which results in decreased tricyclic antidepressant metabolism and increased tricyclic blood levels (toxicity).

Action: Clinicians should use lower doses of drugs that are metabolized through the 2D6 isoenzyme when propafenone is given concurrently.

- Antidepressant levels in plasma should be measured routinely and are especially indicated when unexpected side effects or other findings suggest a possible interaction. Dosages should be adjusted accordingly

Other antidepressants

Amiodarone/Trazodone Significance level 1 (Case Report): Major Advice to Practitioner:

Trazodone, a second generation antidepressant, has been shown to be equal to standard tricyclics in clinical efficacy while causing significantly fewer cardiac side effects.

Action: Consider an alternative agent.

- Caution is recommended in the concurrent use of trazodone and other medications (i.e., amiodarone) known to cause QT prolongation and polymorphous ventricular tachycardia

Warfarin/Trazodone Significance level 2: Moderate Advice to Practitioner:

Trazodone can decrease the PT and PTT when used with warfarin. The mechanism of this interaction is unknown and it is not widely reported.

Action: Monitor PT when adding trazodone to warfarin or stopping trazodone while receiving warfarin.

Digoxin/Nefazodone, Paroxetine Significance level 2: Moderate Advice to Practitioner:

- When nefazodone or paroxetine was added to digoxin therapy, increases in the area under the concentration vs time curve, minimum concentration, and maximum concentration of digoxin have been reported.

- The exact mechanism of this interaction is unknown, however, increases of 15%–30% have been reported. When nefazodone or paroxetine is added to digoxin therapy, digoxin levels should be closely monitored.

- If digoxin is added to nefazodone or paroxetine therapy, no intervention would be required as the dose of digoxin will be determined by serum levels and clinical response.

Action:

- Monitor digoxin levels when adding nefazodone or paroxetine to digoxin or stopping nefazodone or paroxetine in a patient stable on digoxin.

Others

Bupropion/Ciprofloxacin/corticosteroids/theophylline

- Seizure threshold may be reduced

Bupropion/Linezolid

- Monitor for increased serotonergic effects due to weak MAO activity

Duloxetine/Ciprofloxacin

- Increased plasma level of duloxetine due to inhibition of metabolism via CYP1A2

Stimulants

Bretylium/Amphetamines, Methylphenidate, Monoamine Oxidase Inhibitors Significance level 1: Major Advice to Practitioner:

- When used in the treatment of hypertension: the anti-hypertensive effects of bretylium are reportedly blocked or reversed by the concomitant administration of amphetamines, methylphenidate, or monoamine oxidase inhibitors.

- It is not known if the antiarrhythmic effects of bretylium are affected by concomitant use of these drugs.

Action: Carefully observe clinical state when adding these drugs to bretylium.

Antibacterials:Linezolid/stimulants

Linezolide inhibits MAO enzymes

Action:
Discontinue stimulants

Antipsychotics

Ibutilide/Phenothiazines/Haloperidol Significance level 1: Major Advice to Practitioner:

- Ibutilide increases the QT interval, and use with other agents that increase the QT interval is not recommended.
- Newer antipsychotic agents (respiridine, quetiapind) can increase the QT interval and should be used cautiously if at all with ibutilide.
- ction: Avoid the combination if possible

Atropine/Haloperidol Significance level 2: Moderate Advice to Practitioner:

- Worsening of schizophrenic symptoms, decreased haloperidol levels, and tardive dyskinesia have been reported.
- Although this interaction has not been reported with the anticholinergic atropine, a similar interaction is theoretically possible.
- The short half-life of atropine, which is usually used in emergency situations, may make this interaction less likely.

Action: Atropine may be used in emergency situations in patients treated with haloperidol.

Atropine/Phenothiazines Significance level 2: Moderate Advice to Practitioner:

Therapeutic actions of phenothiazines may be decreased by anticholinergics.

- An increase in anticholinergic side effects may be noted.
- The short halflife of atropine, which is usually used in emergency situations, may make this interaction less likely.

Action: Monitor for anticholinergic side effects. Adjust dose of phenothiazines as necessary.

ACE Inhibitors/Phenothiazines
Significance level 2: Moderate Advice to Practitioner:

- Concurrent use of an ACE inhibitor and a phenothiazine (particularly chlorpromazine) can result in synergistic additive pharmacologic effect leading to hypotension and/or orthostasis/postural intolerance.

- When one drug, however, is added to the other, patients should be cautioned about the potential for orthostasis and/or hypotension and the appropriate monitoring techniques should be performed.

Action: Monitor for hypotension and orthostasis when adding one drug to the other.

Warfarin/Chlorpromazine Significance level 2: Moderate Advice to Practitioner:

- Chlorpromazine has been reported to decrease prothrombin times when used with warfarin.

- When warfarin is added to a regimen containing chlorpromazine, no intervention would be required, as the dose of warfarin would be determined by prothrombin times or international normalized ratios.

Action: Monitor PT when adding chlorpromazine, as recommended above.

OTHERS

Quinidine/aripiprazole
- Decreased metabolism od aripiprazole: dose adjustment may be required

amiodarone/aripiprazole
- Increased plasma level of aripiprazole due to inhibited metabolism via CYP2D6

Erythromycin/clarithromycin/aripiprazole
- Increased plasma level of aripiprazole due to inhibited metabolism

Erythromycin/clarithromycin/pimozide
- Decresed clearanve of pimozide to 80%
- Do not combined

Anticonvulsants

Adenosine/Carbamazepine
Significant level 1: Major Advice to Practitioner:

- Adenosine has important interactions with a number of drugs but with psychotropics they do not have notable interaction except for carbamazepine that has the effect of slowing AV conduction.

- When these drugs are prescribed concomitantly, they may act synergistically and lead to a fatal heart block.

Action: Action should be judged on a priority basis as adenosine is mostly administered in critical situations and its half-life is very short (6 minutes).

- In that case no action need be undertaken.

- But if administered for a longer time concomitantly, carbamazepine should be withheld for 4 days prior to the administration of adenosine

Hydrochlorothiazide/Carbamazepine Significance level 2: Moderate Advice to Practitioner:

- Hyponatremia may develop in patients treated with hydrochlorothiazide and carbamazepine.

Action: Monitor for hyponatremia in patients receiving both hydrochlorothiazide and carbamazepine.

If hyponatremia develops, hydrochlorothiazide or carbamazepine should be discontinued or dose decreased.

Nimodipine/Carbamazepine Significance level 2: Moderate Advice to Practitioner:

Plasma concentration of nimodipine may decrease in patients treated with nimodipine and carbamazepine.

Action: Closely monitor nimodipine levels in patients treated with nimodipine and carbamazepine.

Nimodipine/Valproic Acid Significance level 2: Moderate Advice to Practitioner:

- Concurrent use of valproic acid and nimodipine can result in an increase in serum nimodipine concentrations leading to nimodipine toxicity (dizziness, flushing, headache, peripheral edema).

- The mechanism of interaction may be the result of valproic acid inhibition of the first pass metabolism of nimodipine with the resulting increase in nimodipine oral bioavailability.

Action: With concurrent use, patients should be monitored for altered nimodipine effects as valproic acid is initiated, discontinued, or changed in dosage.

Nitroglycerin/Phenothiazine Significance level 2: Moderate Advice to Practitioner:

- Use of nitroglycerin and phenothiazine may result in additive blood pressure reductions.

- This drug interaction may result in problems when a phenothiazine is added to nitroglycerin without anticipating blood pressure reductions.

Action: Monitor blood pressure when initiating the combination.

Warfarin/Carbamazepine Significance level 2: Moderate Advice to Practitioner:

Carbamazepine may increase the metabolism of warfarin, resulting in reduced warfarin activity.

Action: Monitor prothrombin times (PT) or international normalized ratios (INR) as indicated.

Ticlopidine/Carbamazepine Significance level 2: Moderate Advice to Practitioner:

Neurologic symptoms have been seen in association with increased carbamazepine levels because of possible interaction with ticlopidine.

- The mechanism may be active circulating metabolites that complicate the relationship of dose and clinical response.

Action: Monitor clinical state and carbamazepine levels to insure that carbamazepine is not higher than acceptable levels.

Salicyclates/Valproic Acid Significance level 2: Moderate Advice to Practitioner:

- Salicylates may displace valproic acid from protein binding sites. This may result in increased free valproic acid concentration without any change in the total concentration.
- A second mechanism may be that salicylates may alter the metabolic pathways of valproic acid. Because salicylate is highly protein bound, it can be displaced or displace other drugs from binding sites.
- The acetylation of albumin by aspirin could alter protein binding of other drugs and this must be a caution in its use.

Action: Monitoring of valproic acid, total and free concentrations, should be conducted if salicylates are prescribed contemporaneously. Changes in liver enzymes and evidence of valproic acid toxicity should also be monitored.

Benzodiazepines

Digoxin/Benzodiazepines Significance level 2: Moderate Advice to Practitioner:

- If the benzodiazepine is added to the digoxin, increases in digoxin levels may be seen. Since benzodiazepines have differing pharmacokinetic properties, a class interaction cannot be provided.

Action: Monitor digoxin concentrations when adding diazepam or alprazolam (over 0.5 mg daily) in a patient previously stabilized on digoxin

Calcium Channel Blockers (Non-Dihydropyridines)/Benzodiazepines Significance level 2: Moderate Advice to Practitioner:

- Some non-dihydropyridine calcium channel blockers (diltiazem and verapamil) may inhibit the hepatic metabolism of some benzodiazepines (in particular the triazolol benzodiazepines, e.g. alprazolam and triazolam) and increase benzodiazepine concentrations.

- This mechanism appears to be the result of competition for the cytochrome P450 3A4 isozyme.

Action: When combining a non-dihydropyridine calcium channel blocker (diltiazem or verapamil) with a triazolol benzodiazepine (alprazolam or triazolam), monitor the patient's blood pressure and heart rate and watch for increased and prolonged sedative/hypnotic effects.

- Because of the competitive inhibition in the 3A4 isozyme system, clinical efficacy will occur at lower doses.

Warfarin/Chlordiazepoxide Significance level 2: Moderate Advice to Practitioner:

Chlordiazepoxide has been reported to decrease prothrombin times when used with warfarin.

- Action: Monitor PT when adding chlordiazepoxide as recommended above.

Beta blockers

Beta Blockers/Calcium Channel Blockers Significance level 2: Moderate Advice to Practitioner:

- Additive negative inotropic effects may be seen when this combination is used.

Action:

Monitor blood pressure and heart rate frequently when combining these drugs.

Beta Blockers/Phenothiazines Significance level 2: Moderate Advice to Practitioner:

- Each of these agents may inhibit the metabolism of the other.
- Interactions of this type may take a few days to become evident and resolve because effects of the enzyme-altering agent may take a few days to become evident or dissipate.
- If a patient is stabilized on the combination, there is little need to alter therapy.

- Since both of these drugs inhibit the metabolism of the other, enhanced effects of both drugs may be seen when one is added to the other.

- Augmented hypotensive effects of each may be seen.

Action: Monitor clinical efficacy when adding one to the other. The most significant interactions occur with propranolol in combination with chlorpromazine or thioridazine.

Clonidine

Central Antiadrenergic Agents (Clonidine)/Beta Blockers Significance level 1: Major Advice to Practitioner:

- Concurrent use of clonidine and beta blockers can result in synergistic additive pharmacologic effect leading to severe hypotension.

Action: Monitor closely for hypotension and orthostasis when using in combination or adding one drug to the other.

Central Antiadrenergic Agents (Clonidine)/Calcium Channel Blockers (Verapamil) Significance level 1: Major Advice to Practitioner:

- Concurrent use of clonidine and verapamil can result in synergistic additive pharmacologic and toxic effects leading to severe hypotension and atrioventricular (AV) block.
- Action: Monitorclosely for hypotension and orthostasis when using in combination or adding one drug to the other.
- Perform serial ECGs to monitor for development of dysrhythmias (AV block) and discontinue combination therapy if dysrhythmias occur.

Central Antiadrenergic Agents (Clonidine)/Phenothiazines Significance level 2: Moderate Advice to Practitioner:

- Concurrent use of a central acting antiadrenergic agent and a phenothiazine with its alpha-adrenergic blocking activity (particularly fluphenazine) can result in a synergistic additive pharmacologic effect leading to hypotension and in the case of fluphenazine, the development of an acute organic brain syndrome may appear.

- If a patient is stabilized on the combination, there is little need to alter therapy unless an acute organic brain syndrome develops whereby the clonidine should be discontinued.

- When one drug, however, is added to the other,

Action: Patients should be monitored for orthostasis and/or hypotension and followed closely in case an acute organic brain syndrome develops.

Central Antiadrenergic Agents (Clonidine)/Tricyclic Antidepressants Significance level 1: Major Advice to Practitioner:

- Tricyclic antidepressants may inhibit central alpha-2 adrenergic receptors, resulting in a loss of blood pressure control in patients receiving clonidine.
- This may result in severe hypertension, including hypertensive crises. This combination should be avoided whenever possible.
- An alternative antihypertensive or a nontricyclic antidepressant should be used. (This interaction does not occur with the peripheral acting agents such as prazosin).

Action: Avoid this combination whenever possible.

Lithium

Diuretics/Lithium Significance level 1: Major Advice to Practitioner:

- In general, both thiazide and loop diuretics can decrease the renal excretion of lithium and result in lithium toxicity.
- This interaction is well established with thiazide diuretics although it is also possible with loop diuretics.
- Similar interactions with triamterene and spironolactone have been hypothesized.
- Serum lithium levels should be monitored during concomitant therapy.

- If a patient is stabilized on the combination, there is little need to alter therapy.
- If a patient is receiving a diuretic and lithium is added, the lithium dose will be determined by serum levels and clinical response, with little additional intervention required.
- If a diuretic is added to lithium therapy, serum lithium levels may increase and toxicity may result.

Action: Monitor lithium serum levels when a diuretic is added to lithium therapy

Enalapril/Lithium Significance level 2: Moderate Advice to Practitioner:

- Lithium toxicity may result in concomitant administration with enalapril.
- Moderate renal insufficiency or acute renal failure has occurred with this combination.
- The mechanism is not certain, but it is hypothesized that enalapril increases sodium excretion secondary to decreased aldosterone secretion or by altering renal function secondary to ACE inhibition.

Action: Monitor lithium concentrations and decrease lithium dosage if necessary.

Indomethacin/Lithium Significance level 2: Moderate Advice to Practitioner:

- Simultaneous administration of indomethacin or any other nonsteroidal (NSAIDs) and lithium may result in an increase in steady state plasma level up to 40%, and a decrease in renal lithium elimination by 23%. Salicylates did not have this effect when in combination with lithium.

Action: Use aspirin rather than indomethacin or other NSAIDs when the patient is concurrently on lithium.

Lisinopril/Lithium Significance level 2: Moderate Advice to Practitioner:

- Lisinopril may result in more reabsorption of lithium from the renal tubule, and therefore increases serum lithium levels.
- The mechanism may emanate from the ACE inhibitor induced sodium depletion.
- Angiotensin-converting enzyme results in a loss of sodium and fluid volume.
- Given the proposed mechanism of these interaction mechanisms it is likely that all ACE inhibitors may result in lithium toxicity.

Action: If possible, avoid the simultaneous administration of ACE inhibitors and lithium. If the two drugs are used concurrently, then cautious monitoring of lithium levels must be undertaken, with a decrease in the lithium dose as necessary. Use an agent that does not interfere with lithium metabolism.

Losartan/Lithium Significance level 2: Moderate Advice to Practitioner:

- Losartan may increase lithium levels by decreasing lithium's renal excretion and its enhanced absorption.

- Losartan may reduce the renal elimination of lithium. Although this action is not established with other angiotensin-2 receptor antagonists, theoretically they may be expected to have a similar reaction.

Action: Monitor lithium levels, monitor clinical status, and adjust dosage downward as needed.