Psychiatric Side Effects Associated with the Ten Most Commonly Dispensed Prescription Drugs: A Review

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Drugs used to treat medical illness frequently cause psychiatric symptoms or side effects. Careful assessment of possible drug side effects is important to (1) determine whether the condition may be readily reversible by discontinuing the use of a specific drug, (2) avoid inaccurate diagnosis leading to nonindicated psychiatric treatment including additional drug therapy, and (3) identify and characterize previously unrecognized adverse drug effects. Psychiatric side effects of drugs are frequently cited in the *Physicians' Desk Reference* (PDR) and other sources, but there is little or no information on supporting documentation and frequency. The purpose of this review is to examine critically the potential psychiatric side effects of the ten most commonly dispensed drugs. The literature was systematically reviewed (with emphasis on studies conducted in the last 5 years) and a list was formulated of the adverse psychiatric side effect(s) for each drug. An accompanying scale (the literature support scale) was devised to indicate the degree of scientific support for the reported effect. A concise discussion also clarifies the strengths and weaknesses of the support for the occurrence of each adverse effect. The frequency of the reported side effect(s) is provided whenever possible but is often not available or is imprecise (often reflecting certain subpopulations of patients). In addition to the information provided in this review, more subtle psychiatric side effects may go largely unreported.

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Methods

A list of the ten drugs (new and refill prescriptions) most often prescribed in 1988 was taken from the *Pharmacy Times* top 200 drugs of 1988 (Table 1). Two computer literature search systems were used to find the pertinent studies or observations related to psychiatric side effects of these ten drugs: MEDLINE (years 1984 to 1989) and Psyclit (years 1974 to 1989). Some articles were found in more recent publications. Although trade names were used by the *Pharmacy Times*,[1] the literature search was based on the generic active ingredients (which are also listed in Table 1). A literature support scale presented in Table 2 was devised to summarize the weight of scientific evidence supporting each side effect, reflected by the number of asterisks. The most important potential psychiatric side effects are summarized in Table 3.

Commonly Prescribed Drugs

Amoxil

GENERIC—AMOXICILLIN

OTHER COMMON BRAND NAMES—ROBAMOX, TRIMOX (AND OTHERS)

General Information. Amoxicillin is commonly administered at a dose of 250 to 500 mg every 8 hours for adult patients and 20 to 40 mg per kg of body weight every 24 hours for pediatric patients. This semisynthetic penicillin is a bacterial agent that inhibits bacterial cell wall synthesis. Penicillin, therefore, has little effect on eukaryotic cells, which have no cell wall, intracellular organisms, or dormant microorganisms.[2] Clavulanic acid, which is

Table 1. Top 10 Medications Based on New and Refill Prescriptions Dispensed*

Ranking	Drug	Generic Name	Primary Uses
1	Amoxil	Amoxicillin	Antibiotic
2	Lanoxin	Digoxin	Cardiac abnormatalities
3	Xanax	Alprazolam	Anxiety
4	Zantac	Ranitidine	Peptic ulcers
5	Dyazide	Hydrochlorothiazide/ triamterene	Hypertension, edema (2° to congestive heart failure)
6	Tagamet	Cimetidine	Peptic ulcers
7	Tenormin	Atenolol	Hypertension
8	Premarin	Conjugated estrogen	Postmenopausal problems, including osteoporosis
9	Cardizem	Diltiazem	Angina, hypertension
10	Naproxyn	Naproxen	Anti-iinflammatory action

**Information obtained from Pharmacy Times, April, 1989.*[1]

combined with amoxicillin in products such as Augmentin, passes through the cell wall and acts as an inhibitor of beta-lactamase.[3]

POTENTIAL PSYCHIATRIC SIDE EFFECTS†

** Hallucinations
** Confusion
** Mania

Discussion. Overall, there has been little convincing evidence that psychiatric side effects should be a major concern when prescribing amoxicillin. Behavioral changes, including confusion, mania, and hallucinations, may occur rarely in a few susceptible individuals.[4] For example, case reports in 1984 and 1986 found apparent onset of auditory hallucinations with or without visual hallucinations upon start of amoxicillin therapy.[5,6] The 1986 report also noted confusion and manic symptoms in a 30-year-old black woman.[5] This patient had a similar episode when placed on amoxicillin 14 years previously but had no psychiatric reactions to other antibiotics including nonaminobenzyl penicillins. Reversal of symptoms was achieved 9 to 12 days after termination of amoxicillin use.[5] The long time required for recovery after discontinuation of the drug in this case makes a causal relationship more uncertain. In a 1984 case report, interpretation of the cause of visual and auditory hallucinations in an elderly patient was complicated by the patient's cyclothymic history and possible (but clinically inapparent) hypoxia secondary to pneumonia.[6] The hallucinations stopped within 24 hours of drug discontinuation.

In addition to the reports cited above, hyperactivity accompanied by aggressiveness, crying, and insomnia was reported in four children using the closely related drug amoxicillin-clavulanate.[7] Similar effects recurred in a 10-year-old child after restarting amoxicillin-clavulanate 2 months later.[8] It is not known whether amoxicillin alone has these effects on children. While psychotic and anxiety symptoms have been reported with a 0.3% incidence with procaine-penicillin, they were apparently due to the procaine component.[9]

† See Table 2 for an explanation of use of asterisks in the listing of side effects.

Table 2. Literature Support Scale: Possible Psychiatric Side Effects of Drugs

Symbol/Description
* Case report(s) without drug rechallenge
** Case report(s) with confirmation by drug rechallenge
*** Case report(s) plus retrospective studies
**** Placebo-controlled study(s) with patient reports of psychiatric changes (but no formal psychiatric testing)
***** Placebo-controlled study(s) with described psychiatric evaluations or testing
******* Placebo-controlled study(s) with psychiatric testing and drug rechallenge

Note: Asterisks in parentheses such as (*****) indicate very low incidence or lack of statistical suppport despite the nature of the study used.

Lanoxin

GENERIC—DIGOXIN

General Information. Digoxin is commonly used at a dose of 0.50 to 0.75 mg followed by 0.25 mg every 6 to

Table 3. Reported Psychiatric Side Effects of the 10 Most Commonly Dispensed Prescription Drugs

Ranking	Generic Name	Potential Psychiatric Side Effects
1	Amoxicillin	Hallucinations, confusion, mania, hyperactivity (with amoxicillin-clavulanate)
2	Digoxin	Depressed libido, delirium, depression, dementia, psychosis, mania, lethargy
3	Alprazolam	Depression, anxiety (with drug withdrawal), aggressive behavior, mania, changes in libido
4 and 6	Ranitidine and cimetidine	Mania, changes in libido, psychosis, confusion, depression, drug interaction
5	Hydrochlorothiazide/triamterene	Depressed libido, fatigue, SIWI, confusion
7	Atenolol	Decreased arousal and depressed libido, decreased memory, depression, confusion, hallucinations (with paranoia)
8	Conjugated estrogens	Hypomania, changes in sexual behavior
9	Diltiazem	Psychosis, mania
10	Naproxen	Decreased cognitive function

SIWI denotes self-induced water intoxication.

8 hours (to a total dose of 1.0 to 1.5 mg). Intravenous or intramuscular injections are given at an initial dose of 0.25 to 0.5 mg, then 0.25 mg every 4 to 6 hours (to a total dose of 1.0 mg). Maintenance doses are given at 0.125 to 0.5 mg per day orally or 0.125 to 0.250 per day intravenously or intramuscularly. Adjustments in dosage must take into account age, renal function, and lean body mass.[10] The usual pediatric maintenance dose is 10 μg/kg administered every 12 hours.[11] Digoxin is used primarily in the treatment of congestive heart failure, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia.[11] Digoxin increases myocardial contractile force (inotropic effect) by reversible inhibition of sarcolemma Na,K-ATPase, causing enhanced calcium influx.[2,3,11] Digoxin also lowers the conduction rate of the AV node by indirectly increasing parasympathetic tone and depressing sympathetic tone.[3] Potentially severe cardiac consequences, including heart block and arrhythmias, are well-recognized adverse effects.[5,6] In addition, nausea, headache, fatigue, anorexia, abdominal pain, vomiting, and abnormal color perception have been noted.[5,6]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

**** Depressed libido
*** Delirium
*** Depression
* Dementia
* Hallucinations and psychosis
* Mania and hyperactivity
* Lethargy

Discussion. Although the adverse cardiac effects of digoxin are well known, it is less commonly recognized that digoxin has numerous neuropsychiatric side effects.[12,13] For example, a retrospective study at the Mayo Clinic reported approximately a 2% to 3% incidence of adverse psychiatric side effects occurring between 1958 and 1962, which included delirium, depression, and personality changes.[13] About a 7% to 8% incidence of psychiatric side effects was found between 1940 and 1944.[13] It should be taken into account, however, that these early reports, limited by their unsophisticated retrospective design, allowed potential bias.

The elderly appear to be more susceptible to adverse (including psychiatric) effects of digoxin than other population groups.[14–17] They experience both increased end-organ sensitivity to digoxin and altered pharmacokinetics with increasing age.[14] Digoxin half-life in patients over 80 years of age is about 70 hours, compared with 30 to 40 hours in younger patients.[14] Delirium and psychosis have been noted in numerous case reports and range from mild disorientation to violent agitation with hallucinations.[13–19] Psychosis can occur in patients receiving

long-term digoxin therapy when dosage is increased and disappears with dose reduction,[20] indicating that the psychiatric side effects of digoxin are dose-dependent. Rechallenge with higher digoxin dosage was not attempted in these cases.

While hyperactive states have occasionally been reported,[12,21,22] lethargy and depression are likely side effects of digoxin.[12,13,15,17,21,23] Digoxin-induced depressive states have been misdiagnosed as primary depression.[20] Rose[24] postulated that this effect of digoxin may be related to alteration in hypothalamic Na, K-ATPase activity.

Most cases of adverse psychiatric effects of digoxin appear to have occurred at toxic levels of the drug; however, many toxic effects occur in the therapeutic range. Two cases have recently been reported in which patients with normal therapeutic levels of digoxin (0.5 to 2.0 ng/mL) had impaired cognitive function (tested by a cognitive capacity screening test), depression, and anorexia.[17] Within 3 days of discontinuation of the drug, these symptoms returned to normal.

In a long-term controlled study, potential sexual side effects of digoxin were investigated using questionnaires and patient interviews.[25] Results showed a significant decrease in sexual desire and frequency in the digoxin-treated group of patients. The mechanism of this change did not appear to be due to alterations in androstenedione or dehydroepiandrosterone, as their plasma levels were unchanged by digoxin.[25]

Although most of the evidence for psychiatric effects of digoxin consists of retrospective and case studies, the number of reports is rather striking, including many other older reports of the effects of digitalis on behavior that have not been mentioned here. Taken together with a long history of investigation, it appears that physicians should take special note of the potentially serious psychiatric side effects of digoxin.

Xanax

GENERIC—ALPRAZOLAM

General Information. Alprazolam is commonly prescribed in doses of 0.25 to 0.5 mg orally, three times daily (up to 4 mg each day).[11] This drug is primarily used as an antianxiety agent, though antidepressant effects have also been claimed.[2,11] Although many mechanisms for its CNS depressant action have been proposed, it appears likely that it increases the effect of GABA as an inhibitory neurotransmitter.[3]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

(******) Depression
****** Anxiety, delirium and paranoid reaction with drug withdrawal
(******) Aggressive behavior
*** Libido changes

Discussion. It is perhaps not too surprising that a drug such as alprazolam that is used for psychiatric purposes also appears to have numerous potential adverse neuropsychiatric side effects. This is because such a drug must be effective in reaching and altering the central nervous system (CNS) for its therapeutic (and therefore adverse) effects. Naturally, in these and the other reports of psychiatric side effects of alprazolam, observations are complicated by previous psychiatric illnesses in addition to the difficulty in statistical approaches. However, it is clear from the many studies cited herein that adverse psychiatric side effects of alprazolam must be considered in the differential diagnosis of behavioral changes that occur in patients recently put on or taken off the medication.

In 1987, in a placebo-controlled study of 46 patients with panic disorder receiving 3 to 10 mg of alprazolam per day, as many as 33% developed DSM-III criteria for major depression.[26] However, because many patients with panic disorder have comorbid major depression, it is problematic in this study as to whether the depression was a true "side effect" or whether treatment with alprazolam unmasked an underlying depressive disorder. In fact, the incidence of depression appears to be much lower, as indicated in a much larger (n = 263) 1988 multicenter placebo-controlled study in which only one patient was found with apparent depressive side effects at comparable dosage.[27]

Aggressive or manic behavior in three patients was also noted in the multicenter study cited above.[27] Numerous independent case reports also indicate that alprazolam can cause manic and aggressive behavior in both men and women.[28–33] In one case report, alprazolam at 0.5 mg three times daily had little effect on aggressive behavior, as did alcohol alone, but a combination of the two produced aggressive dyscontrol.[29] In most reports, however, there is no mention of alcohol use. Manic symptoms did not occur until dosage was increased to 2 mg, diminished considerably when reduced to 0.75 mg, and then reappeared when a 1.5 mg dose was given.[30]

Changes in libido may also occur with alprazolam use.[26,34–36] In a retrospective study of 32 patients treated with alprazolam, 15 had decreased libido while four reported increased sexual desire.[37] Other cases of decreased libido have also been reported.[35,36] Decreased sexual desire and orgasm appear to be dose-dependent and to recover with dose reduction.[35]

Case reports and placebo-controlled studies indicate that rebound anxiety can occur upon withdrawal of al-

prazolam.[37–39] While it is difficult to distinguish withdrawal symptoms from reemergence of an original disorder, withdrawal anxiety occurs even in patients who receive alprazolam for reasons other than anxiety disorder. In one placebo-controlled study of 126 patients, 27% of patients treated for panic disorder reported rebound panic attacks and 13% had rebound anxiety when their dosage of alprazolam was reduced by 2 to 10 mg. Several case reports have also suggested that delirium[40] and paranoid reactions[41] can occur with alprazolam withdrawal, even when tapering is gradual.[42]

Zantac, Tagamet

GENERIC—RANITIDINE; CIMETIDINE

General Information. Ranitidine is commonly administered in one 150-mg dose every 12 hours, while cimetidine is administered in a 300-mg dose 3 to 4 times per day.[7,11] These drugs are used in the therapy of duodenal (and some gastric) ulcers, Zollinger-Ellison syndrome, and for prophylaxis of stress ulcers (eg, after surgery, burns, and trauma).[2,11] Ranitidine and cimetidine decrease the concentration and volume of acid secreted by gastric parietal cells by acting as histamine H_2-receptor antagonists. Cimetidine (more than ranitidine) is also known to inhibit hepatic cytochrome P-450 and P-448 mixed-function oxidase (MFO) enzyme systems, thereby altering the metabolism of certain drugs.[7]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

** Mania and aggressiveness
** Sexual dysfunction including decreased libido
(******) Confusion, delirium, or psychosis
* Depression

Discussion. There are many reports (mostly case reports) of H_2-receptor antagonists having adverse psychiatric side effects. The elderly and those with serious medical illness appear to be at highest risk. Mania, including aggressive behavior, has been particularly noted[43–49] a few days after initiating treatment, with return of adverse symptoms with drug rechallenge.[43,48] A few cases of depression have also been noted, although no drug rechallenge results have been reported to help confirm this possible effect.[50–53]

Confusion, delirium, and psychosis secondary to use of these H_2-receptor antagonists have also been reported. Case studies have noted confusion with ranitidine[45,54–57] and cimetidine[53,56–63] especially in the elderly.[57] In a small placebo-controlled trial, no instances of confusion were noted with ranitidine use,[64] but negative results are not surprising given the low incidence of this adverse effect. Psychosis with auditory and visual hallucinations with use of these drugs has also been reported.[53–66] For example, a 72-year-old woman reported visual hallucinations when ranitidine therapy was initiated.[65] Supportive evidence was provided when symptoms, including both auditory and visual hallucinations, returned with drug rechallenge. Psychosis can also occur in younger patients, as with a 14-year-old girl with no history of a psychiatric disorder or drug abuse who had hallucinations 3 days after cimetidine treatment was started.[66] The effect was reversed within 24 hours of discontinuing the drug.

Sexual dysfunction with decreased libido, as well as impotence and gynecomastia, have been noted in several cases with cimetidine use.[68–70] This effect appears to be dose related. Rechallenge leads to recurrence of sexual dysfunction.[70] While doses used to treat duodenal ulcers do not appear to cause impotence, in a study of 22 men on high dose cimetidine (3.5 times the amount used in duodenal ulcer therapy), about 50% subjectively reported sexual problems secondary to drug therapy even though only three men had abnormal nocturnal penile tumescence.[68]

In addition to the studies cited above, cimetidine (probably because of its increased effect on hepatic P-450 and P-448 MFO systems) poses potential problems with drug interactions that may be of psychiatric importance.[62,71–74] For example, the combinations of 300 mg three times per day of cimetidine with 0.375 mg of triazolam at bedtime produced both visual and auditory hallucinations in a 49-year-old woman, presumably as a result of decreased clearance of the triazolam.[74] Other reports, particularly of decreased metabolism of tricyclic antidepressants in the presence of cimetidine, indicate the need for monitoring drug levels.

Although initial studies with H_2-receptor antagonists did not reveal significant adverse neuropsychiatric side effects,[57,58] the widespread use of these drugs has led to numerous reports of many potential psychiatric symptoms that may occur (particularly with cimetidine) in susceptible patients. Most studies were case reports, but many appeared to be substantiated by rechallenge of the drug to produce similar behavioral change(s). In light of these observations and the popular use of these agents, further study would prove helpful to clarify and quantify these potential adverse reactions.

Dyazide

GENERIC—HYDROCHLOROTHIAZIDE (25 MG) AND TRIAMTERENE (50 MG)

OTHER COMMON BRAND NAME—MAXZIDE

General Information. Hydrochlorothiazide/triamterene is commonly administered at one to two capsules per day (maximum four per day).[11] The drugs are used primarily to treat hypertension, and also for edema caused by congestive heart failure or cirrhosis of the liver.[11] Hydrochlorothiazide (HCTZ) and triamterene act as diuretics by inhibiting sodium reabsorption (and hydrogen and potassium secretion) in the cortical collecting tubule (and distal convoluted tubule in the case of hydrochlorothiazide).[3,11] Thus water and sodium are secreted, with potassium being retained due to the action of triamterene. It is this potassium-sparing effect that is the primary reason for the addition of triamterene.[2] Hyperkalemia is a major side effect, and serum potassium must be monitored.

POTENTIAL PSYCHIATRIC SIDE EFFECTS

**** Decreased libido
**** Fatigue
(***) Self-induced water intoxication (in psychiatric patients)
* Confusion

Discussion. Psychiatric effects are not a major concern with hydrochlorothiazide/triamterene, and few studies have been published in this area. There appears to be no substantial evidence for triamterene-stimulated psychiatric symptoms. In addition, no significant cognitive alterations were found in 24 adolescents on therapy with hydrochlorothiazide 25 to 50 mg three times per day.[76] However, other antihypertensive agents are often known to be associated with sexual dysfunction, and such dysfunction occurs with HCTZ as well.[76] Decreased subjective sexual function was documented in 5 of 12 hypotensive men with no history of sexual dysfunction in a small placebo-controlled trial of HCTZ.[77]

Fatigue is not a psychiatric problem per se, but it can be a symptom of depression. In a postmarketing surveillance study of over 47,000 patients treated with triamterene/hydrochlorothiazide (Maxzide), no significant psychiatric changes were noted except for a 2% to 3% incidence of fatigue.[75]

An association of HCTZ use and self-induced water intoxication (SIWI) in schizophrenic and other psychiatric patients has been discussed in the literature.[77,78] In a large retrospective study of psychiatric patients with polydipsia, HCTZ therapy was often noted.[78] Although HCTZ probably does not cause SIWI, it may exacerbate the hyponatremia caused by SIWI, usually in combination with some degree of syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to psychiatric medications or psychosis itself.

Although the side effects of delirium and confusion are not well supported in the literature, they may occur in HCTZ overdose. For example, confusion and delirium were observed in a 65-year-old man with end-stage renal disease,[79] perhaps because this diuretic is cleared primarily by renal mechanisms. In considering the psychiatric aspects of these drugs, it is also very important to note that HCTZ therapy can raise lithium levels dangerously. For example, in an elderly woman on lithium treatment for manic depressive episodes, lithium levels reached a near lethal concentration (3.9 mg/L) causing changes in her mental status after HCTZ was started.[80] The mechanism probably relates to the inverse relationship between sodium and lithium levels. Thus, depressed sodium concentration caused by HCTZ results in enhanced lithium levels. Overall, these reports suggest that therapy with hydrochlorothiazide/triamterene could cause unexpected behavioral changes, but much more documentation is needed to clarify the incidence of these adverse reactions.

Tenormin

GENERIC—ATENOLOL

General Information. Atenolol is administered at doses of 50 to 200 mg per day.[2,11] This drug is an antihypertensive agent that is also used for angina pectoris, arrhythmias, migraine headaches, and essential tremor.[2] The beta-adrenergic blocking action of the drug competes with sympathetic neurotransmitters for receptor sites, thereby causing depression of sympathetic tone.[3]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

**** Sexual dysfunction including decreased libido and arousal
(****) Memory loss
* Confusion, delirium, hallucinations

Discussion. Although infrequently, atenolol may cause memory loss, hallucinations, and sexual problems. In several small controlled studies, atenolol produced no apparent adverse psychiatric changes such as anxiety, depression, or altered memory.[81–86] In one of the studies, however, mild but statistically significant decreases in memory acquisition and short-term and long-term memory were noted.[84] Short-term memory loss and psychotic behavior were also noted in a 1983 case report, but drug rechallenge was refused.[87]

Physicians should inquire about sexual dysfunction in patients using atenolol. In a 1988 placebo-controlled study, atenolol appeared to produce both short-term (1 to 4 weeks) and long-term (1 year) sexual dysfunction in libido, erection, and ejaculation.[88] The possibility that some patients are vulnerable to atenolol-induced sexual dysfunction has been supported by other investigations, including both retrospective[89] and controlled studies.[90] An apparent decreased state of arousal has also been reported.[91,92] For example, a 6-week, placebo-controlled study involving 16 patients found (by questionnaire) depressed arousal secondary to use of 100 mg of atenolol per day.[91]

Cases of other psychiatric side effects, such as confusion, paranoia, and visual hallucinations, have also been reported.[87,91–94] Although adverse neuropsychiatric effects are often found to be more frequent with the lipophilic β-blocking agents such as propranolol than with hydrophilic agents like atenolol,[2] others feel that all beta-blockers cause cognitive dysfunction and sedation with equal frequency.[86]

Premarin

GENERIC—CONJUGATED ESTROGEN

OTHER COMMON BRAND NAMES—PROGENS

General Information. This estrogen is administered at a dose of 0.3 to 1.25 mg per day for 1 to 23 days of the 28 day menstrual cycle.[2] For abnormal uterine bleeding, 25 mg is given intravenously or intramuscularly. Conjugated estrogen is often used for postmenopausal problems such as osteoporosis.[2,3] It is also used for female menopausal symptoms, atrophic vaginitis, prostatic carcinoma, and hormonally induced uterine bleeding.[2,3] Estrogens stimulate the synthesis of specific proteins in responsive tissues by binding to specific cell receptors.[3] Hypocalcemia may occur with estrogen use.[3] Endometrial cancer is also thought to be increased by unopposed estrogen.[3,95]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

**** Alteration of sexual behavior
* Hypomania
* Panic attacks

Discussion. Because conjugated estrogen is generally used in postmenopausal women as a replacement therapy, it is not surprising that associated behavioral or psychiatric effects of menopause such as depression are actually helped by this drug.[96] Estrogen treatment appears to influence sexual behavior and in most cases helps to reduce psychosexual problems in estrogen-deficient women.[97,98] Estrogens probably have little or no direct effect on sexual desire in women, but may indirectly enhance feelings of femininity.[99] In at least one bilaterally castrated male, satisfactory sexual activity has been maintained by the use of estrogen.[100]

Case reports have suggested that hypomania[96] or panic attacks[101] can also occur with estrogen use. In cases of panic attack, symptoms abated after discontinuation of the drug.[101]

Cardizem

GENERIC—DILTIAZEM

General Information. Initially, diltiazem is administered at 30 mg each morning and night, and then at up to 360 mg per day.[3,11] Diltiazem is used mainly to treat angina pectoris and hypertension.[3,11] Diltiazem is a benzothiazepine that acts by inhibition of the slow-channel calcium.[2,11] By blocking calcium entry into myocardial cells, it produces a direct negative inotropic action, dilates peripheral and coronary arteries, and prevents coronary artery spasm.[2,3,11]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

* Psychosis and hallucinations
* Mania or hyperactivity

Discussion. Several studies indicate that calcium channel blockers such as diltiazem may actually have therapeutic uses in psychiatric illness, particularly mania.[102,103] The scientific documentation for possible psychiatric side effects of diltiazem consists of only a few case studies. Drug-induced psychosis has been reported, one case with associated manic features[104] but without drug rechallenge.[104,105] Diltiazem-induced mania was reported in another case,[106] but drug rechallenge reported later did not appear to confirm the original finding.[107,108] Overall, therefore, it appears that diltiazem is a relatively safe drug with regard to potential adverse psychiatric side effects.

Naprosyn

GENERIC—NAPROXEN

General Information. Naproxen is used at 250 to 500 mg two times per day.[11] This agent is used primarily for arthritis, gout, and other forms of musculoskeletal inflammation.[2,10] Naproxen is one of the nonsteroidal anti-inflammatory drugs (NSAIDS) that affect many cellular and subcellular processes. Although the precise mechanism of action of these drugs is still unclear, they are

known to inhibit cyclooxygenase, which depresses the synthesis of prostaglandins and thromboxanes from the arachidonic acid precursor.[3]

POTENTIAL PSYCHIATRIC SIDE EFFECTS

* Decreased cognitive function

Discussion. There appears to be little support in the literature to suggest that naproxen has significant adverse psychiatric effects. In a controlled study of over 1000 patients, no mention was made of significant psychiatric complaints.[109] Potential decline in cognitive skills was suggested, however, in a recent study of 12 elderly patients.[110] In this 3-week investigation (using naproxen, 750 mg) diminished cognitive skills were noted in one or more tests in five patients. Further study will be needed, however, to confirm this observation and to determine whether the elderly are at increased risk. When considering psychiatric issues it is important to note that naproxen has been reported to cause increased lithium levels within 5 days in a study of seven patients,[111] suggesting that patients on lithium may need decreased lithium dosage and close monitoring when naproxen is also used in therapy.

Key words. Prescriptions, drug.

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