

WYOMING DRUG UTILIZATION REVIEW

July 2005



Edited by
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Children, Antidepressants, and Suicidality

Stephen Brown, MD

In October, 2004, the FDA after a split committee vote of 15 to 8 required a “black-box” warning on antidepressants in the pediatric population. The warning noted that antidepressants increased suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder and other psychiatric disorders. The antidepressants reviewed were fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), venlafaxine (Effexor), citalopram (Celexa), fluvoxamine (Luvox), and nefazodone. This warning has created some reevaluation for many physicians and considerable debate. The warning has been applied to all antidepressants.

Clearly antidepressants have helped many youth. From 1992 until 2001 the rate of suicide in 10 to 19 year olds dropped by 25% across the nation. This decrease coincided with the significant increase in the use of the newer antidepressants in youth. However Medco Health Systems

has reported that antidepressant prescriptions for patients younger than 18 years fell 10% in 2004 after rising by almost the same amount in 2003. The steepest declines occurred in the second half of 2004 with the discussions about and implementation of the black-box warning. This is of significant importance in Wyoming given our routinely high suicide rates across all age groups.

The information¹ the FDA used to base their decision for the special warning came from the pooling of 24 studies with 9 antidepressants and over 4400 youth. The studies’ data and gathering of information was not designed to assess the development of suicidality and the definition of such varied considerably. The data suggested that youth treated with a pill placebo had a risk of 2% of developing suicidality. Youth treated with therapy alone had a 40% increase in suicidality over placebo and youth treated with the newer antidepressants had a 4% increase in suicidality,

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Wyoming Medicaid Preferred Drug List

PPIs (Effective 2/1/05)

OTC Prilosec (omeprazole)
Protonix (pantoprazole)

Long-Acting Opioids (Effective 2/1/05)

Methadone
Morphine Sulfate

2nd Generation Antihistamines (Effective 3/1/05)

Loratadine / Loratadine-D

Statins (Effective 7/1/04)

Lescol
Pravachol (pravastatin)

NSAIDs (Effective 7/1/04)

Ibuprofen
Naproxen

Skeletal Muscle Relaxants (Effective (2/1/05)

Cyclobenzaprine

ACE Inhibitors (Effective 2/1/05)

Captopril
Enalapril
Lisinopril

Calcium Channel Blockers (Effective 2/1/05)

Verapamil
Plendil (felodipine)

To learn more about the Wyoming Medicaid Preferred Drug List, visit the PDL website at www.uwyo.edu/PDL.

roughly twice the rate as placebo. It is important to understand that in these studies no youth completed suicide in the 4400 children involved in the study.

The data did not specify whether the increase in suicidality correlated with the development of akathisia, mania, hypomania, or other side effects that can be induced by antidepressants. However there is also no proven causal link between these medication risks and suicidality.

Of all the antidepressants, only fluoxetine has an FDA labeled indication to treat pediatric depression. In one recent study² comparing cognitive behavior therapy (CBT), fluoxetine and placebo, 439 adolescents with depression were studied for twelve weeks. In this study suicide-related ideation and self-harm-behaviors dropped dramatically in all groups. High-risk patients were excluded but about one-fourth of patients reported at least some degree of suicidal ideation at the start of the study. The group that received a combined CBT and fluoxetine treatment showed a 71% response rate, those with fluoxetine alone had a 60.6% response rate, CBT alone a 43.3% response rate and a pill placebo a 34.8% response rate.

The American Academy of Child and Adolescent Psychiatry recommends that, as always, practitioners take all steps necessary to protect the well being of their patients. Informed consent should include the risk of suicidality with antidepressants with a discussion of warning signs to monitor at home. The AACAP presently suggests following the frequency of follow-up visits suggested by the FDA. The frequency they recommend is weekly the first month, biweekly the second, once after twelve weeks and then as clinically indicated. The effectiveness of a weekly monitoring program or whether phone contact or clinical assessments by other clinicians such as therapists and nurses would be sufficient has not yet been proven.

Generally given the data, fluoxetine and/or cognitive therapy would be the first line treatment at this time. In

general the optimum treatment would consist of both an antidepressant and therapy. The FDA did not contraindicate the use of any antidepressants so the next consideration generally would be another SSRI should the first line treatment fail or be contraindicated. The FDA also now requires that a Medication Guide regarding many of these risks and what to watch for be given by the pharmacy with every prescription of antidepressants for children and adolescents.

Taking the time for a thorough assessment of psychiatric concerns including an interview of the child alone is paramount. Follow-up visits need to assess suicidal risks. The physician may wish to access the American Psychiatric Association and AACAP website to help them with these details at www.parentsmedguide.org/physiciansmedguide.htm. Parents would benefit by information on depression, antidepressant risks and other child psychiatric illnesses by accessing www.parentsmedguide.org/parentsmedguide.htm.

The three leading causes of death in adolescents nationwide are motor vehicle accidents, homicide and suicide. It still is important to attentively target the treatment of youth depression. The AACAP Work Group on Research strongly supports the treatment of children and adolescents with depression despite the risks. The greatest risk in childhood depression may be doing nothing.³

References

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2. March J, et al; Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA* 2004;292:807-820.
3. Brent D: Antidepressants and pediatric depression-the risk of doing nothing. *NEJM* 2004;351 (October 14):1589-1601.

Prescriber Response Forms

(2004)

The Wyoming Drug Utilization Review Program sends out 6 cycles of education letters to prescribers each year. Each prescriber who receives an education alert letter is asked to complete and return a response form. In the response form, we ask the prescriber to classify the information in the alert letter as *useful*, *neutral*, or *not useful*.

The graph on page 3 shows the following information: the return rate for prescriber response

forms for 2004, the percentage of returned provider response forms that fall into each of the 3 classifications (*useful*, *neutral*, and *not useful*), and the percentage of *no classification*, which is assigned if the provider fails to classify the information in the alert letter. Response rates are over 50% and responses are coded as either *useful* or *neutral* by over 50% of the respondents.

Elidel® and Protopic® Associated with Potential Cancer Risk

Jamie Cronebaugh, PharmD

Pimecrolimus (Elidel®) and tacrolimus (Protopic®) are topical agents indicated for the treatment of eczema by suppressing the immune system. On March 10, 2005 the FDA issued a public health advisory to health care professionals who prescribe pimecrolimus and tacrolimus. They advised prescribers to use only as directed and only after other eczema treatments have failed to work because of the potential cancer risk associated with their use.¹

The FDA will be adding a black box warning to Elidel® and Protopic® packaging to warn about an increased risk of certain cancers, especially among children. The FDA cited post-marketing reports of tumor-related adverse events associated with these drugs, including skin cancer, lymphoma, and precancerous lesions. They also noted that these products are being aggressively marketed as a safe, long-term alternative to steroid therapy and are being prescribed inappropriately to young children.¹

This action follows the recommendations made by the FDA's Pediatric Advisory Committee during its February 15, 2005 meeting, when findings of cancer in three different animal specials were reported. Data showed that the risk of cancer increased with the amount of drug given. The data also included a small number of reports of cancers in children and adults treated with Elidel® or Protopic®.¹

The FDA's Public Health Advisory advises physicians to weigh risks and benefits of these drugs in adults and

children and consider the following when prescribing Elidel® and/or Protopic®¹:

- Both products are approved for short-term and intermittent treatment of atopic dermatitis (eczema) in patients unresponsive to, or intolerant of other treatments.
- Neither product is approved for children < 2 years old.
- Both products should only be used short-term, and not continuously, as the long-term safety of these products is unknown.
- Neither product should be prescribed to any patient with a weakened or compromised immune system.
- Use only the minimum amount needed to control the patients' symptoms.

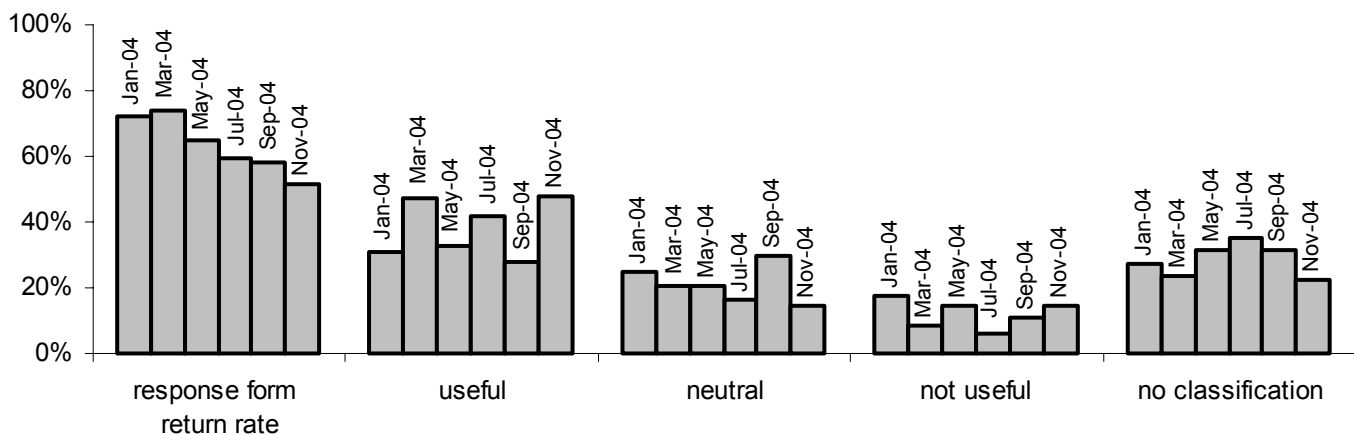
Manufacturers of Elidel® and Protopic® have agreed to conduct research to determine whether there is an actual risk of cancer in humans.

References

1. FDA talk paper: FDA issues public health advisory informing health care providers of safety concerns associated with the use of two eczema drugs, elidel and protopic. U.S. Food and Drug Administration [2005 Mar 10]: [1 screen]. Available from: URL: <http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html>
2. In brief: Elidel and protopic. Med Lett Drugs Ther 2005; 47(1205):25.

Prescriber Response Form Statistics

(2004)



Amiodarone: Guidelines for Use

Christopher Meyer, PharmD

Raquel Romero, PharmD

Introduction. Amiodarone is a complex class III antiarrhythmic agent with multiple electrophysiologic effects. It prevents the recurrence of life-threatening ventricular arrhythmias and sudden death. This drug is very potent with many possible toxicities associated with its use. It also has many drug interactions that need to be monitored for, especially with warfarin and digoxin. With all of this in mind, amiodarone is a very effective drug if it is used properly and continually monitored.

Pharmacokinetics. Amiodarone is an iodine-containing compound similar to thyroxine. Its bioavailability is poor; however, absorption is enhanced when the drug is taken with food. Amiodarone is highly lipid soluble and therefore is stored in the fat, muscle, liver, lungs, and skin. Desethylamiodarone (DEA) is the major metabolite. Amiodarone has an elimination half-life average ~58 days.

Electrophysiologic Effects. Amiodarone prolongs QT interval, slows heart rate and atrioventricular nodal conduction (via beta receptor and calcium channel blockade). It also prolongs refractoriness via the potassium and sodium blockade, and slows intracardiac conduction.

Indications

1. FDA approved for emergency room treatment of ventricular tachyarrhythmias.
2. FDA approved for long-term treatment of secondary prevention of life-threatening ventricular arrhythmias.
3. Not FDA approved but still used for the treatment of atrial fibrillation.

Dosing Guidelines

Life-Threatening Arrhythmia

IV, inpatient treatment

150mg IV bolus over 10 minutes, if needed bolus can be repeated after 10-30 minutes, then 1 mg/min for 6 hrs, then 0.5mg/min for 18 hrs, then reduce IV dose or convert to oral dosing if possible.

Side Effects: hypotension, bradycardia, and atrioventricular block

Ventricular Arrhythmia

Oral, inpatient treatment

800-1600 mg/day in divided doses, until a total of 10 g has been given; then 200-400 mg/day

Side Effects: bradycardia, QT prolongation, GI upset, constipation, and rarely Torsades de pointes

Atrial Fibrillation

Oral, inpatient or outpatient treatment

600-800 mg/day in divided doses, until a total of 10 g has been given; then 200 mg/day

Side Effects: bradycardia, QT prolongation, GI upset, constipation, and rarely Torsades de Pointes

Toxicities. Amiodarone has been associated with toxicities involving the lungs, thyroid gland, liver, eyes, skin, and nerves. The toxicities are associated with the dosage and duration of treatment with amiodarone. It is important for physicians to dose below 300 mg/day and aim at 200 mg/day or less for maintenance therapy.

Pulmonary Toxicity. Pulmonary toxicity is the most serious potential adverse effect. The most common clinical presentation is cough and progressive dyspnea with patchy infiltrates on the chest radiograph and a decrease pulmonary function test. If any of these signs/symptoms occur, amiodarone must be stopped and supportive care measures must be done.

Thyroid Toxicity. Thyroid toxicity is the most common complication that requires treatment. Hypothyroidism is 2-4 x more common than hyperthyroidism. If hypothyroidism occurs, amiodarone may be continued; however, thyroid supplementation must be done. If hyperthyroidism occurs, removal of amiodarone is warranted if possible, the addition of antithyroid medications or prednisone, and surgical thyroidectomy.

Liver Toxicity. Liver toxicity is seen in patients who are receiving long-term amiodarone therapy. Patients are rarely symptomatic; however, if their liver enzymes are 3X higher than normal, amiodarone should be discontinued unless their risk for a recurrent life-threatening arrhythmia is high.

GI Toxicities. GI toxicities include: nausea, vomiting, anorexia, and constipation which are often dose related and usually improve once the dose is reduced.

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Neurologic Toxicities. Neurologic toxicities can include ataxia, paresthesias, and tremor. These conditions are often dose related. Peripheral neuropathy occurs at a rate of 0.3% annually.

Ocular Toxicities. Corneal deposits are visible on examination in nearly all patients taking amiodarone. Once these deposits are noted, it is important to discontinue the drug before progression of the toxicity occurs. Optic neuropathy, optic neuritis, and total blindness have been noted, therefore, it is important to continue eye exams and discontinue the drug if any abnormalities are noted.

Dermatologic Toxicities. Skin discoloration is common in patients using amiodarone. Patients should be cautioned to use sun block and avoid direct sun exposure for extended periods of time. The blue-gray discoloration will resolve over several months after amiodarone is discontinued.

CV Toxicities. Possible cardiovascular adverse effects associated with amiodarone usage include bradycardia, heart block, proarrhythmia, and hypotension. Torsades de Pointes occurs rarely; however, precautions must still be taken. Amiodarone is contraindicated in patients with a 2-3 degree heart block who do not have a pacemaker. If amiodarone is administered IV, and CV toxicities arise, it must be discontinued or the rate of the infusion should be reduced.

Drug Interactions. Amiodarone is a potent inhibitor of hepatic and renal metabolism of several drugs. It inhibits CYP2C9, CYP2D6, and CYP3A4. Interactions with

warfarin (increased bleeding) and digoxin (increase levels) are the most significant. It can also interact with simvastatin (increased myopathy), sildenafil (increased levels), cyclosporine (increased levels), other antiarrhythmic drugs, quinolones, and antidepressants (increase amiodarone levels). Also, it is important to counsel patients not to eat grapefruit, because it can inhibit the conversion of amiodarone to its active metabolite.

References

1. Siddoway LA. MD, Amiodarone: Guidelines for use and monitoring. American Family Physician; Clinical Pharmacology. December 2003. Vol 68. N11; Pg 2189-96.
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3. Hansten PD, Horn JR. Drug Interactions analysis and management. Vancouver: Applied Therapeutics;1998.
4. Singh BN. Amiodarone: The expanding antiarrhythmic role and how to follow a patient on chronic therapy. Clin Cardiol 1997;20:608-18.
5. Pollack PT. Clinical organ toxicity of antiarrhythmic compounds: ocular and pulmonary manifestations. Am J Cardiol 1999; 84:37R-45R.
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7. Pacerone (amiodarone) product information. Upsher-Smith Laboratories, Inc; 1998.

Amiodarone: Monitoring

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Due to the number of reports to the FDA of serious adverse events with amiodarone, it is recommended that all patients on amiodarone be reviewed for appropriate monitoring. The monitoring form on page 6 has been developed to assure that a mechanism is in place for documenting the monitoring requirements. The form can be accessed at <http://www.vapbm.org/monitoring/amiodaron.htm>.

The information on this form is a compilation of recommendations and may be modified according to clinical practice at the facility. If there already is an adequate monitoring system in place at the facility, it is not necessary to implement this form.

Amiodarone: Monitoring Form

This form is available at
<http://www.vapbm.org/monitoring/amiodaron.htm>

Examination	Baseline	3 months	6 months	12 months	If Symptoms
Pulmonary Function^a					
Chest X-ray^b					
Thyroid Panel^c					
Liver Panel					
ECG					
Eye Exam					
CBC					
Chem-7					
Clinical Evaluation					

^a Baseline only if underlying pulmonary disease suspected

^b Others have recommend monitoring every 3 to 6 months

^c Some recommend monitoring every 6 months, others periodically

Potential Drug Interactions	Date Started ^a	Date lab f/u:	Date lab f/u:	Date lab f/u:
Warfarin		INR:	INR:	INR:
Digoxin		Digoxin:	Digoxin:	Digoxin:
Antiarrhythmic:		Level:	Level:	Level:
Phenytoin		PHT:	PHT:	PHT:
Cyclosporine or Tacrolimus		Level:	Level:	Level:

^a Table may be used to document appropriate follow-up when amiodarone or interacting medication initiated

Medications Known to Interact with Amiodarone ^a	Interaction	Recommendations
Warfarin	↑ PT and INR (usually begins within 1 week, stabilizing after 1 month) due to inhibition of warfarin metabolism; ↑ bleeding risk	Consider ↓ warfarin dose by 33-50%; monitor INR weekly for 4 weeks; titrate to goal INR
Digoxin	↑ digoxin concentrations (usually within 1-7 days, progressing over several weeks or months) by ↓ renal and nonrenal clearance; may result in toxicity	Consider ↓ digoxin dose by 50%; monitor digoxin at 2 and 6 weeks; titrate to therapeutic digoxin level
Antiarrhythmic agents (quinidine, procainamide, flecainide)	↑ antiarrhythmic blood levels (within 5-7 days, taking several weeks for maximum effect) due to ↓ hepatic clearance; may prolong impulse conduction resulting in arrhythmias	Monitor ECG intervals; ↓ dose of antiarrhythmic 33-50% (20-33% for procainamide) several days after start of amiodarone or if already on amiodarone, initial dose of antiarrhythmic should be ↓ by 50% of the usual initial dose; or monitor serum concentrations and adjust dose accordingly
Phenytoin	↑ concentrations of phenytoin (usually within 3-4 weeks) by inhibition of hepatic metabolism; may result in toxicity	Monitor phenytoin serum concentrations at 2-4 weeks and adjust dose accordingly; amiodarone levels may ↓
Cyclosporine, Tacrolimus	Clearance ↓ by 50%; may result in toxicity (renal dysfunction)	Monitor plasma concentrations frequently and adjust dose accordingly
β-adrenergic blockers, Calcium antagonists (diltiazem, verapamil)	Possible potentiation of bradycardia, sinus arrest, AV block	Observe patient carefully for signs of cardiac toxicity

^a Clinically significant interactions listed; for additional drug interactions, refer to references below.

References

- Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver:Applied Therapeutics; 1998
- Singh BN. Amiodarone: The expanding antiarrhythmic role and how to follow a patient on chronic therapy. Clin Cardiol 1997;20:608-18.
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- Pacerone® (amiodarone) product information. Upsher-Smith Laboratories, Inc; 1998.

Dose Conversion to Felodipine from Other Dihydropyridine Calcium Channel Blockers

Brittney Parks, PharmD

One challenge of a preferred drug list is safely and effectively converting patients to the preferred agent. Limited data exists to guide the dose conversion between calcium channel blockers.

Nifedipine to Felodipine. One study¹ has examined a conversion from immediate-release nifedipine to felodipine. The method of conversion is described in Table 1 below. This conversion illustrates that clinical judgment is still important when converting from one agent to another. For example, patients taking 60 mg/day of nifedipine can be converted to either 5 or 10 mg/day. The focus of this study was not the safety and efficacy during the transition.

Amlodipine to Felodipine. More studies have looked at the conversion of amlodipine to felodipine with differing results. In all studies, the initial transition was made using an identical dose of felodipine to that of amlodipine.²⁻⁵ However, at the conclusion of three of the trials, the average felodipine dose was statistically higher after titration for efficacy.²⁻⁴ After conversion to felodipine, two studies showed an inferior control of hypertension based on blood pressure² or a statistical increase in additional cardiovascular medications.³ Regardless, converting between equal doses of these agents appears to be a reasonable starting place.

The conversions to felodipine discussed are guidelines for the initial transition. Although these agents are in the dihydropyridine structural class of calcium channel blockers, pharmacologic and pharmacokinetic differences in the agents exist, so an individual may not necessarily respond identically to the agents. Because the published results of conversion to felodipine vary, the conversion should be approached on a patient-by-patient basis.

References

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2. Blivin SJ, Pippins J, Annis LG, Lyons F. A comparative analysis of amlodipine and felodipine in a military outpatient population: efficacy, outcomes, and cost considerations. *Mil Med* 2003;168:530-535.
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4. Manzo BA, Matalka MS, Ravnal SL. Evaluation of a therapeutic conversion from amlodipine to felodipine. *Pharmacotherapy* 2003;23(11):1508-1512.
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Nifedipine dose (mg/day)	Equivalent felodipine dose (mg/day)
30	5
60	5-10
80-120	10

Table 1. Dose conversion between nifedipine and felodipine. Adapted from 1

Wyoming Drug Utilization Review

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