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Food and Drug Administration (FDA) Issues Urgent Recall Of Injectable Drugs

The Food and Drug Administration (FDA) on January 25, 2001, issued an urgent recall of 38 injectable drugs marketed by Phyne Pharmaceuticals of Scottsdale, Arizona. Another company, AMRAM Incorporated, of Rathdrum, Idaho, manufactured these products for Phyne, which was AMRAM's sole customer.

Last December 14, AMRAM notified Phyne that it was recalling these products because they were manufactured under substandard conditions. The nationwide recall followed FDA's inspections of both Phyne Pharmaceuticals and AMRAM Inc. During the inspections, the FDA found violations of Good Manufacturing Practices manufacturing guidelines for pharmaceuticals. These guidelines are intended to help ensure that drug products are safe and effective and, in the case of injectables, sterile.

The FDA urges that anyone possessing any of these products should contact and return them to Phyne Pharmaceuticals at 7950 East Red Field Rd., Scottsdale, AZ 85267, (800) 345-3391 or 480-998-4142, FAX (480) 443-4775. Some of the products are labeled with both companies' names; however, some may bear one or the other company's name as manufacturer or distributor with or without the other company being identified. All lot numbers and codes, strengths and sizes and expiration dates are included in the recall. A list of the recalled products appears at the end of this article.

Some of the drugs on the list have legitimate therapeutic uses, such as colchicine, a very old drug used to treat gout. However, judging from the nature of a majority of the others it is most likely that medical consumers would be exposed to risk from these substandard products in the offices of complementary-alternative-medicine practitioners. It appears from a conversation we had with the FDA that chiropractors are among Phyne's largest customers.

A number of these "drugs" are quite interesting historically. Their use was discredited decades ago but they are now reappearing as "cutting-edge" complementary-alternative-medicine treatments. Descriptions of a few follow:

- *Pangamic acid* is the 1951 apricot -pit

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creation of E. T. Krebs, Jr. who called it vitamin B-15 and promoted it to increase tissue oxygen levels and for numerous other situations, none of which have been substantiated. In fact, there is no evidence that pangamic acid is a vitamin. Krebs, an apricot-pit guru, was also the inventor of the quack cancer cure laetrile from apricot pits.

• *Procaine* is a very old local anesthetic that originally went by the brand name NOVOCAINE. In 1956, Professor Anna Aslan and her colleagues at the Parhon Institute of Geriatrics, in Bucharest, Romania, claimed remarkable beneficial effects in a wide range of disorders, including reversing of the aging process, from the intramuscular injection of procaine (which they called "H3" and hyped in some countries, including the U.S., as Gerovital H3). The claims have not been supported by any scientifically valid evidence or subsequent trials carried out by other researchers.

• Extract from the adrenal glands of cattle, sheep and pigs is sold as *adrenal cortex extract* by Phyne Pharmaceuticals. The FDA directed the removal of all products containing adrenal cortex from the market in January 1978 because of the substantial risk of under-treatment of serious conditions, such as adrenal cortical insufficiency, burns, and low blood sugar, when adrenal cortex extract was used. Adrenal cortex extract brought Phyne to public attention in September 1996 when the FDA issued an alert on this dangerous and unapproved drug after reports that at least 54 people had contracted serious bacterial infections after receiving the Phyne product. Seventeen patients had to have abscesses drained surgically.

The Centers for Disease Control and Prevention (CDC) reported in August 1996 that 68 patients had received the adrenal cortex extract from a Denver doctor who was promoting the product for weight loss. Adrenal cortex extract is also promoted on the Internet for a wide variety of other conditions such as

All Lot Numbers/Codes and Expiration Dates Are Included In the Recall:

Adenosine Monophosphate, 25 mg / mL, 30 mL vial

Ascorbic Acid Injection, 500 mg / mL, 50 mL vial

Beet Ascorbic Acid Injection, USP-500 mg / mL, 50 mL vial

Biotin, 10 mg / mL, 30 mL Injection

Chlorpheniramine Injection, (strength and size unknown at this time)

Choline Chloride, 30 mL vial

Colchicine, .5 mg / mL, 30 mL multi-dose vial

Dexpanthenol, 250 mg / mL, Injection preserved, 30 mL vial

Diphenhydramine, 30 mL vial

Disol, USP Brand of EDTA, 150 mg / mL, 100 mL vial

Echinacea (2X) Homeopathic Injection, 30 mL multi-dose vial, contents per mL 1:1 Macerated (2X)

Edetate Disodium Injection, USP, 3g / 20mg (150 mg / mL), 20 mL vial

Endocrine, 30 mL vial—Note: this product was also distributed as Adrenal Cortex Extract (ACE) 30 mL

Folic Acid, 10 mg / mL, 30 mL Injection

Germanium Sesg., 15.5 mg / 30 mL Injection (Sesguloxide, USP)

Glycyrrhizen, 30 mL vial

Human Chorionic Gonadotropin for Injection, 10,000 units, 10 mL multi dose vial

Hydrochloric Acid, 2 mg / mL, 100 mL vial

Hydrogen Peroxide, 11 cc per 100 mL vial

Hydroxocobalamin, 30 mL vial

Iron 59 Injection, 30 mL vial. Each cc contains:
- Ferrous Gluconate 5.9 mg
- Cobalt Gluconate 9 mg
- Cyanocobalamin 5 mg
- Procaine HCL 10 mg

(L) Glutathione, 60 mg / mL, 30 mL vial

L-Taurine Injection, 50 mg / mL, 100 mL vial & 30 mL vial

Liver Injection, Crude, 30 mL multiple dose vial

Lypo-Vite Injection, 30 mL multi-dose vial. Each mL contains:
- Cyanocobalamin 100 mcg
- Riboflavin 5 mg
- Phosphate Sodium 5 mg
- Thiamine HCL 50 mg
- Pyridoxine HCL 5 mg
- d-Panthenol 5 mg
- Ascorbic Acid 50 mg
- Choline Chloride 100 mg
- Insitol 50 mg
- DL-Methionine 25 mg
- Benzyl Alcohol 1.5%

Magnesium Chloride Injection, 200 mg / mL, 50 mL multi-dose vial

M.I.C. 50mL vial. Each 2 mL contains:
- L-Methionine 50 mg
- Inositol 100 mg
- Choline Chloride 100 mg
- Benzyl Alcohol 1.5%

MIC with Folic Acid, 50 mL vial

Niacin, 30 mL

Pangamic Acid, 500 mg / mL, 30 mL vial

Procaine Hydrochloride Injection, USP, 2%, 100 mL multi-dose vial

Pyridoxine HCL (B-6), 100 mg / mL 30 mL Injection

Riboflavin, 30 mL vial

Sodium Thiosalicylate, 30 mL Injection

Superoxide Dismutase (S.O.D.), 10 mg / mL, 30 mL multi-dose vial

Thiamine HCL, 100 mg / mL, 30 mL Injection B-1, 100 mL vial & 200 mg / mL

Thymus Extract, 10 mg / mL, 30 mL multi-dose vial

Vitamin B_{12} (cyanocobalamin)

low energy levels, aging, chronic fatigue, and stress, to name a few. The CDC said that 47 of these patients developed abscesses in either the arm or the buttocks, depending on what site was used for the injection. They also reported that five persons the doctor injected with extract in Wyoming also developed abscesses. A second Denver doctor reported two similar cases.

We are not aware of any patients becoming infected from the Phyne products involved in the current recall. However, there were three patients injured in Philadelphia after receiving injections of colchicine. Injectable colchicine is given in a dose of 0.5 milligrams per milliliter, but the Phyne product was mistakenly produced in a concentration of 5 milligrams per milliliter, 10 times more concentrated than it should have been.

Phyne's ethical culture and disregard for the public's safety is revealed in their notification to the FDA on January 29, 2001 that the company is not recalling vials of injectable adrenal cortex extract. How can Phyne blatantly ignore the FDA's recall or for that matter continue to sell a drug that was banned in 1978?

In a face-off with the FDA, it appears that the agency is unsure if they have regulatory authority over many Phyne products. Products such as adrenal cortex extract, thymus extract, and pangamic acid injection may fall under the dangerously pro-quackery Dietary Supplement Health and Education Act (DSHEA) of 1994 and be considered dietary supplements. If this is the case, for all practical purposes, these products are unregulated and the FDA can do nothing, leaving consumers totally on their own. For this the public has the United States Congress to thank.

There is added concern about the source of glandular cow parts used to make, for example, thymus extract and the adrenal cortex extract injectables in light of the possibility that cows used are from countries where bovine spongiform encephalopathy (BSE or "mad cow" disease) exists. We do not believe that the FDA has adequate resources or regulatory authority to ensure that dietary supplement producers are not importing and using BSE-infected cow parts.

BUYER BEWARE!

What You Can Do

If a complementary-alternative-medicine practitioner, including a chiropractor, recommends an injection, especially a dietary supplement injection, grab your money and run.

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New Safety Warning For the Alzheimer's Disease Drug Rivastigmine (EXELON)

In the January 2001 issue of *Worst Pills, Best Pills News* we recommended that the new Alzheimer's disease drug rivastigmine (EXELON), the third such drug on the market, should not be used for at least five years. This would be April 2005. The two other Alzheimer's drugs available in the U.S. are tacrine (COGNEX) and donepezil (ARICEPT).

On January 26, 2001, Novartis Pharmaceuticals Corporation notified health professionals that new warnings are being added to the professional product labeling or "package insert" concerning the risk of severe vomiting when rivastigmine treatment is stopped for some reason and then restarted at a later date.

In the controlled clinical trials conducted before the drug was cleared for marketing, 47 percent of patients treated with a rivastigmine dose in the range of 6 to 12 milligrams per day developed nausea. This figure compared to 12 percent of those receiving an inactive or dummy (placebo) drug. In all, 31 percent of the rivastigmine-treated patients developed at least one episode of vomiting compared to 6 percent of the placebo-treated patients. Vomiting was rated as severe in 2 percent of rivastigmine-treated patients.

There has been one report, since the drug was approved, of severe vomiting with rupture of the esophagus (the tube that connects the mouth and stomach) after restarting treatment with rivastigmine in a dose of 4.5 milligrams following eight weeks off the drug. The following information in bold type has been added to the drug's package insert:

WARNINGS

Gastrointestinal Adverse Reactions

Exelon ® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia [loss of appetite]**, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID** [two times a day] **and titrated** [slowly increased] **to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose after 8 weeks of treatment interruption).**

Our well-known "five-year-rule" says you should not use a new drug until it has been on the market for at least five years because pre-market testing does not provide a large enough "statistical universe" to make it likely that hidden hazards will show, as has been the case with rivastigmine.

What You Can Do

If you or a family member who has been prescribed rivastigmine has had it stopped, make sure that if it is restarted that the dose is not greater than 1.5 milligrams two times a day.

The Italian Drug Glucosamine (XICIL) In the Treatment Of Osteoarthritis

An excellent Belgian study appearing in the January 27, 2001 issue of the highly respected British medical journal *The Lancet* found that glucosamine (XICIL) was more effective than an inactive dummy pill, or placebo, in relieving the symptoms of osteoarthritis. Glucosamine may also have a positive effect in modifying the course of osteoarthritis compared to no treatment at all. The study was funded by the manufacturer of Xicil.

Glucosamine is a pure substance made in Italy that is synthesized from chitin and is a defined mixture of glucosamine, sulphate, and sodium chloride. Sodium and chloride together are table salt. Chitin is a long chain of glucosamine (a type of sugar) molecules linked together and referred to as a polymer. It is similar in chemical structure to cellulose or vegetable fiber. Chitin makes up the hard outer skeleton of beetles, crabs, and certain microorganisms. Glucosamine is also present in human cartilage and joint fluid.

The Belgian study involved 212 people with a diagnosis of osteoarthritis of the knee who were at least 50 years of age. Xicil powder was

mixed and taken as an oral solution in a dose of 1,500 milligrams once daily by 106 patients, while the other 106 received an identical placebo. Only about two-thirds of the patients in each group completed the full three years of the study.

There were two primary outcome measures in the study. The first was joint structural changes which measured the average joint-space width using x-rays in order to determine if glucosamine would affect the course of joint damage seen in osteoarthritis. Increased narrowing of the joint-space over time is believed to indicate progressive damage to the joint from osteoarthritis.

The symptoms of osteoarthritis as perceived by the patients was the second outcome and was assessed using what is known as the Western Ontario and McMaster Universities questionnaire. This form, frequently used in osteoarthritis research, asks five questions about joint pain, two about stiffness, and 17 about limitations of physical function.

The 106 patients who received placebo treatment had progressive joint-space narrowing after three years while there was no significant narrowing in the Xicil group. The authors concluded that the glucosamine mixture in Xicil could modify the course of osteoarthritis. More on this later.

A positive effect was also seen on the symptoms of osteoarthritis in the Xicil group compared to those receiving the placebo. Based on the questionnaire used in the study, symptoms worsened slightly in patients receiving the placebo compared to the improvement seen in those taking Xicil.

The results of this study cannot be translated to the numerous unregulated glucosamine products sold in health food stores and pharmacies in this country. Because glucosamine can be sold as a dietary supplement under the Dietary Supplement Health and Education Act of 1994, manufacturers of glucosamine products and other dietary supplements are not required to follow pharmaceutical-type Good Manufacturing Practice (GMP) guidelines. Such GMPs ensure that what is listed on the label is in fact in the bottle and, among other things, tablets and capsules consistently disintegrate and dissolve rather than passing straight through the body without being absorbed.

The Council for Responsible Nutrition, a trade group representing largely unregulated dietary and herbal supplement producers in the U.S., is having a field day trying to piggyback results for Xicil, which is regulated as a drug in Italy, to the products sold by their members that are not required to adhere to pharmaceutical type GMP guidelines. Although the Council maintains that its members follow GMPs, they fail to mention that the GMPs that they follow are food GMPs that only require supplements to be produced in relatively clean facilities, not the more stringent pharmaceutical GMPs.

We have several caveats concerning the interpretation of the Belgian study. First, even though the glucosamine that was used in Xicil is regulated as a drug in Italy and some other European countries, not all drug regulatory authorities are equivalent to the FDA. In many European countries, Germany for example, the manufacturer and content of natural products is regulated but these products have never been reviewed for effectiveness. Since Europe has no Freedom of Information Act, the public has no way of knowing what the basis was for allowing glucosamine to be sold for osteoarthritis. There may be none.

Second, the boundaries between science and promotion have been blurred. It is no longer possible to accept at face value the veracity of data from published clinical trials—even those appearing in the most prestigious medical journals such as *The Lancet*. What is required is a rigorous review process that is open to the public, something that is lacking even in this country.

Third, the process by which osteoarthritis damages joints is not fully understood. In an editorial accompanying the study, it was suggested that imaging techniques other than x-rays of the joint-space may be more valid indicators of the progression of osteoarthritis. Right now, all that can be said is that Xicil may prevent the x-ray evidence of progression of osteoarthritis, which may be different than actually preventing the progression of the disease.

The National Institutes of Health is sponsoring a large study of glucosamine and chondroitin in the treatment of arthritis. This study will not be completed until March 2005. We strongly support this type of drug development research.

What You Can Do

You should avoid using dietary and herbal supplements until they are regulated by the FDA. Until then it is let the buyer beware.

Major Breakthroughs In the Prevention and Treatment Of High Blood Pressure

The beginning of the new millennium was marked by the publication of the results of randomized clinical trials about two "breakthrough, novel and innovative" interventions for the prevention and treatment of high blood pressure. Randomized clinical trials are the scientific "gold standard" for assessing the effectiveness of all types of medical interventions. Neither of these breakthroughs requires a doctor's visit nor a trip to the pharmacy. Both save rather than cost money and there are no known adverse effects associated with their use.

The first study was supported by the National Heart, Lung, and Blood Institute, a part of the National Institutes of Health, and was published in the January 2, 2001 issue of *Annals of Internal Medicine*. It was called Trials of Hypertension Prevention, Phase II (TOHP II) and involved 1,191 subjects who were randomly assigned to one of four intervention groups: (1) weight loss only; (2) salt (sodium) reduction, only; (3) combined weight loss and sodium reduction; and (4) as a control group usual care. Eligible participants were overweight adults who were not receiving drugs to treat high blood pressure or taking drugs that would increase their pressure. They had to have a diastolic blood pressure (lower number) of 83 to 89 millimeters (mm) of Mercury (Hg) and a systolic blood pressure (upper number) of less than 140 mm Hg.

Subjects assigned to the weight loss groups had a goal of losing 10 pounds during the first six months of the study. They started with an individual counseling session, and then attended 14 weekly group meetings led by dietitians or health educators, then six biweekly group meetings and finally monthly group meetings. In addition to cutting calories, physical activity was increased gradually to 30 to 45 minutes per day.

The average amount of weight lost for the weight loss groups was 9.7 pounds after six months, 4.8 pounds at 18 months, and at 36 months the amount of weight lost was 0.4 pounds. The average weight gained in the control group receiving usual care at the same times was 0.2, 1.5, and 4.0 pounds, respectively. This translated at 36 months to a 0.35 mm Hg reduction in diastolic and a 0.45 mm Hg reduction in systolic blood pressure per 2.2 pounds (one kilogram) of weight lost.

The researchers also assessed the likelihood of the trial subjects developing high blood pressure. High blood pressure was defined for the purpose of this study as a systolic pressure 140 mg Hg and a diastolic pressure of at least 90 mm Hg. Using this definition, those assigned to the weight loss group were significantly less likely than the controls receiving usual care to develop high blood pressure. The risk of developing high blood pressure at 6, 18, and 36 months and at the end of the study was reduced by 42, 22 , 19 and 21 percent, respectively in the weight loss group.

The second study was also supported in part by the National Heart, Lung, and Blood Institute and was published in January 4, 2001 issue of the *New England Journal of Medicine*. This trial goes by the acronym DASH standing for the Dietary Approaches to Stop Hypertension diet.

The DASH diet emphasizes fruits, vegetables, and low-fat dairy products. It includes whole grains, fish, poultry, and nuts, contains only small amounts of red meat, sweets and sugar containing drinks, and has decreased amounts of total and saturated fat and cholesterol. This type of diet has been shown previously to lower blood pressure in those with and without high blood pressure compared to a typical diet in the U.S.

Clinical trials have shown that limiting the quantity of salt in typical diets in the U.S. or northern Europe reduces blood pressure. Guidelines recommend reducing the amount of salt in the diet to one-fifth of an ounce (5.8 grams of sodium chloride, 1 ounce = 28.35 grams) a day.

The researchers wanted to know if reducing the level of salt from the average American diet of 8.7 grams to below the currently recommended upper limit of 5.8 grams would reduce blood pressure more than reducing salt intake only to the recommended limit of 5.8 grams.

Participants, 412 in total, were randomly assigned to eat either a typical U.S. diet or the DASH diet. Within each group the participants ate food with high, intermediate, and low levels of salt for 30 consecutive days, in random order.

Participants assigned to the DASH diet showed a significantly lower systolic blood pressure at each level of salt intake (high, intermediate, low). The difference was the greatest with high salt intake compared to low salt intake. Blood pressure can be lowered in both those on a typical U.S. diet and the DASH diet by reducing salt intake.

Another remarkable finding from this study was that according to the study's authors, in participants with high blood pressure the combined effects of the DASH diet plus a low level of salt intake were greater than or equal to treatment with any of a variety of different single high blood pressure lowering drug. It is equally remarkable that the effects seen in this trial took place in only 30 days. The combination of low salt intake with the DASH diet was well tolerated by the participants.

It is unlikely that you will see direct-to-consumer TV ads or glossy maga-

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Review of Anti-Seizure Drugs For Bipolar Disorder

The editors of the highly respected *Medical Letter on Drugs and Therapeutics*, for doctors and pharmacists, reviewed evidence from controlled clinical trials of anti-seizure drugs for psychiatric disorders in the December 11, 2000 issue. Controlled clinical trials are the "gold standard" for testing the effectiveness of drugs. Anti-seizure drugs are widely used in treating bipolar disorder (also known as "manic-depressive illness"), and we will focus here primarily on their use for this disorder.

Patients diagnosed with bipolar disorder have mood swings that alternate between periods of extreme highs (mania) to severe lows (depression). These swings are out of proportion to, or totally independent of, everyday events, and affect thoughts, feelings, physical health, behavior and normal functioning.

No single pattern of symptoms fits every sufferer, but there are four distinct types of mood episodes that can occur in the course of the illness:

1. *Mania (manic episode)* often begins with a pleasurable sense of heightened energy, creativity and social ease—feelings that without proper medical treatment can quickly escalate into a full-blown manic episode. At this point, people typically lack self-awareness, deny that anything is wrong, and angrily blame those who point out a problem.

2. *Hypomania (hypomanic episode)* is a milder form of mania with less severe symptoms and less overall impairment. For example, the individual may have an elevated mood, feel better than usual, and be more productive. During these episodes patients often feel good—so good, in fact, that they may stop taking their medication.

3. *Depression (major depressive episode)* takes away one's capacity to experience pleasure and causes profound sadness and irritability, changes in sleep patterns, a decrease in appetite, inability to concentrate, low self-esteem, and thoughts of suicide. Severe episodes also may include hallucinations or delusions.

4. *Mixed episode* is perhaps the most disabling since an individual can experience both mania and depression simultaneously or at different times throughout the day.

The two most important types of drugs to control symptoms of bipolar disorder are antidepressants and mood stabilizers. When certain anti-seizure drugs are used to manage the symptoms of bipolar disorder they are termed mood stabilizers.

Lithium (ESKALITH, LITHOBID, LITHONATE) is the standard primary treatment for bipolar disorder, but it can cause severe toxicity, requiring monitoring of blood levels, and is not effective in some patients. Mood stabilizers are the mainstay of long term preventive treatment for both mania and depression and are used to improve symptoms during acute manic, hypomanic and mixed episodes. The mood stabilizers reviewed in *Medical Letter* are divalproex (DEPAKOTE), carbamazepine (TEGRETOL), lamotrigine (LAMICTAL), gabapentin (NEURONTIN), and topiramate (TOPAMAX).

Divalproex (DEPAKOTE)

The enteric-coated form of divalproex is the only drug approved by the Food and Drug Administration (FDA) for treatment of bipolar disorder, specifically for manic episodes associated with this condition.

According to *Medical Letter*, the response to this drug was 48 percent, compared to 49 percent with lithium and 25 percent with a placebo (dummy drug) in a 21-day study of 179 patients hospitalized for acute mania. Smaller studies have confirmed that about half of patients with acute mania respond to divalproex, whether or not they had previously responded to lithium. One 12-month study involving 372 patients found no difference in the time before symptoms recurred whether divalproex, lithium or placebo was administered.

The professional product labeling ("package insert") for divalproex carries the strongest warning the FDA can require, a "black box" warning, informing doctors and pharmacists about potentially fatal toxicity to the liver and pancreas associated with use of this drug. In the September 2000 issue of *Worst Pills, Best Pills News* we covered the strengthening of divalproex's black box warning regarding potentially fatal toxicity to the pancreas.

Carbamazepine (TEGRETOL)

This drug is FDA-approved for specific types of seizure disorders and the severe bursts of facial pain seen with the condition known as trigeminal neuralgia.

Medical Letter found that carbamazepine may be useful in patients who do not respond to, or

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BREAKTHROUGHS, *from page 22*

zine promotions touting weight loss and reducing daily salt intake to treat or prevent high blood pressure because the only one that would profit from these steps is you.

What You Can Do

You may be able to prevent on your own or treat your high blood pressure, in consultation with your doctor, by instituting the type of dietary lifestyle changes tested in these two clinical trials.

BIPOLAR, *from page 23*

cannot tolerate, lithium or divalproex. Carbamazepine has been less effective than lithium for maintenance treatment of bipolar disorder, but a combination of carbamazepine and lithium may be more effective than either drug alone.

Carbamazepine's package insert carries a black box warning concerning bone marrow toxicity that can lead to a loss in production of blood cells.

Lamotrigine (LAMICTAL)

Lamotrigine is approved by the FDA, along with other drugs, for the treatment of seizure disorders.

A clinical trial in 192 patients found lamotrigine more effective than a placebo for bipolar depression. *Medical Letter* termed lamotrigine about as effective as lithium for the treatment of acute mania and marginally more effective than a placebo when used alone in patients who cycle rapidly between mania and depression.

Like divalproex and carbamazepine, lamotrigine carries a black box warning in its package insert. This one concerns serious rashes than can require hospitalization and discontinuation of treatment that have been reported with the use of lamotrigine. These rashes have included the life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis. We reported on the requirement for lamotrigine's black box warning in the May 1997 issue of *Worst Pills, Best Pills News*.

Dispensing errors have occurred when the anti-fungal drug terbinafine (LAMISIL) was erroneously dispensed by pharmacists instead of LAMICTAL (see the August 2000 issue of *Worst Pills, Best Pills News*).

Gabapentin (NEURONTIN)

Gabapentin is FDA-approved for seizure disorders along with other anti-seizure drugs. It was found to be less effective than lamotrigine and no more effective than placebo in a small controlled trial in patients with refractory mood disorders.

The most common adverse effects of gabapentin are dizziness, somnolence (drowsiness) and other symptoms and signs of central nervous system (CNS) depression. Patients are warned not to drive a car or operate complex machinery until they have gained sufficient experience with the drug to gauge whether or not it affects mental or motor performance adversely.

Topiramate (TOPAMAX)

This drug is FDA-approved for seizure disorders in conjunction with other anti-seizure medications.

Controlled clinical trials have not been conducted using topiramate in the treatment of bipolar disorder, though uncontrolled case reports do appear in the literature suggesting that topiramate may be useful in managing this illness.

Adverse effects most often associated with topiramate have been related to the CNS. In adults, the most significant adverse effects fall into two general categories: (1) psychomotor slowing, difficulty with concentration, and speech or language problems (in particular, difficulty finding words); and (2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances such as irritability and depression.

Medical Letter observed that, except for divalproex in the treatment of acute mania (an FDA-approved use), the effectiveness of anti-seizure medications for the treatment of psychiatric illness, including bipolar disorder, has not been well established by controlled clinical trials. Still, the mood stabilizing effects of these drugs may be useful.

Most of the prescribing of anti-seizure drugs for bipolar disorder and other psychiatric illness is termed "off-label" as these uses have not been approved by the FDA. Only FDA-approved uses can appear on a drug's package insert, which is why non-approved use is said to be off-label.

A study published in a medical journal, even a well-known one, is no substitute for the FDA's drug approval process. Medical journal editors must accept the veracity of data submitted for publication, but the FDA has the responsibility of ensuring that data used by agency scientists and outside advisory committees in approving new drugs or new uses for old ones are valid. To complicate matters now, intense competition in the pharmaceutical marketplace has blurred the once-sharp boundaries between medical journal articles and promotional hype by drug companies.

What You Can Do

If you are being treated for a psychiatric disorder, or a member of your family is, and the use of an anti-seizure drug is being considered as a mood stabilizer, you should discuss the risks and potential benefits of these drugs with your doctor if they are going to be prescribed for an off-label use.