



# Health Matters May 2008; Volume 2, Issue 8

## Manufacturer Recalls of Heparin Products

On January 17, 2008, Baxter International Inc. voluntarily recalled nine lots of multiple-dose vials of concentrated heparin product due to nearly 350 reported adverse events, including 19 deaths. The adverse events included difficulty breathing, GI distress, angina, tachycardia, abnormal sensations of the skin, throat swelling, bleeding and rapidly falling blood pressure that led to life-threatening shock. 40% of the reported adverse events were classified as severe. These adverse events were primarily seen in patients who had received bolus doses of heparin during hemodialysis.<sup>1,2</sup> Further evaluation revealed that similar events were observed in patients who were undergoing invasive cardiac surgery and photophoresis. Consequently, on February 28, 2008, Baxter expanded its recall to include all concentrated vials, (both single- and multi-dose, as well as HEP-LOCK flush solutions) until more was known about all heparin products.<sup>2</sup>

Upon the initial recall, Baxter and the Food and Drug Administration (FDA) revealed that the recalled heparin products contained a heparin-like contaminant in its active pharmaceutical ingredient or API. The API that Baxter uses to manufacture its heparin products is produced and imported from a pharmaceutical plant in China. This heparin-like contaminant is structurally similar to heparin and was not recognized in the solution until special testing was developed by the FDA.<sup>3</sup> On March 19, 2008, the FDA announced that they had identified the contaminant to be an altered form of an oversulfated chondroitin sulfate which was not a natural byproduct of the heparin manufacturing process: it is still unknown if the contaminant was intentionally added to the heparin.<sup>4</sup> The FDA will not definitively say if this contaminant is the true cause of the adverse events either, but is believed to be causative by association.<sup>5</sup>



Baxter manufactures nearly 50% of all United States heparin products. However, heparin is still being manufactured by APP Pharmaceuticals and Hospira. These companies are currently undergoing FDA tests and inspections to determine if their heparin products contain API or contaminants similar to the Baxter product.<sup>4</sup> On March 21, 2008, the manufacturing firm B. Braun recalled 23 lots of their premixed heparin IV solutions, believing that they may have received some of the contaminated API as well.<sup>6</sup> Baxter has stated that its production of heparin products will not resume until all information is collected and the manufacturer can ensure a safe product. The FDA still maintains that it does not anticipate a future shortage of heparin production as the other manufacturers are capable of maintaining the heparin supply.<sup>2</sup>

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## Chantix: A Word of Caution

On February 1, 2008, the FDA issued a warning in response to reports of neuropsychiatric symptoms in patients taking varenicline (Chantix®), a partial agonist of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor used for smoking cessation.<sup>1</sup> The reported symptoms include agitation, behavioral changes, depression, suicidal ideations, and suicide attempts. Some of these psychiatric episodes were reported in clinical trials, but it appears that further awareness has occurred during post-marketing surveillance.<sup>2</sup>

Nicotine withdrawal alone has previously been associated with exacerbations of underlying psychiatric disorders. Although the role of varenicline in neuropsychiatric conditions is not well understood, side effects have been observed in as little as a few days after initiating treatment. Typical varenicline dosing is 0.5 mg daily for the first 3 days, then 0.5 mg twice daily on days 4 to 7 through which the patient may continue smoking. From day 8 to the end of treatment, 1 mg twice daily is given and the patient is instructed to stop smoking.<sup>1</sup> The recommended duration of treatment is 12 weeks. Reported cases have involved patients with and without a history of psychiatric disorders, as well as patients who are taking varenicline and those who have stopped taking varenicline.<sup>2,3</sup>



In light of these concerns, the FDA has recommended that health care professionals monitor patients for changes in mood or behavior. Patients should let their doctors know if they experience any of the symptoms listed above. The FDA is currently working with Pfizer to create a patient medication guide, and the FDA has asked the manufacturer to increase the prominence of the neuropsychiatric adverse events in the *Warnings & Precautions* section of the prescribing information.<sup>3</sup> New warnings include the statement: “serious psychiatric illness” were not included in pre-marketing studies and varenicline’s safety in this group has not been determined.<sup>1</sup> At this time, the FDA has not advised practitioners to discontinue prescribing varenicline.

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## Hormone Replacement Treatment Skews Mammogram Results

Hormone Replacement Therapy (HRT) is commonly prescribed for the relief of menopausal symptoms in the United States. Over 25 million women receive a prescription every year for such therapies. Hormones may help counteract bothersome symptoms of menopause, including hot flashes and vaginal dryness, and may also possibly protect against osteoporosis.

Important new information suggests that women should consider more than just symptom relief before starting hormone therapy. The Women’s Health Initiative enrolled over 16,000 patients and released their findings in 2002. This study showed that women who take HRT have a slightly higher rate of breast cancer: increased by 1 out of 1000 women. Additionally, studies have shown that women taking hormones have an increase in breast tissue density. This effect may be profound in older women whose breasts usually become less dense with age. Studies have demonstrated that the denser the breast tissue, the more difficult the mammogram results are to interpret. This may have a significant impact on the sensitivity and accuracy of mammogram reports. In a trial published by the Archives of Internal Medicine, 35% of women on HRT received abnormal mammogram results compared to 23% of patients taking placebo. Physicians ordered breast biopsies more often in women on HRT (10%) compared to those on placebo (6%). Interestingly, despite higher numbers of breast cancers in the HRT group, biopsies performed in this group less frequently diagnosed cancer.

Women are strongly encouraged to consider the risks and benefits of HRT before initiation of treatment. Women should be appropriately counseled on HRT before even short-term use and this counseling should include the impact on mammogram results and interpretations, as well as the potential for a decreased ability to detect cancer. Researchers are recommending that women get a baseline mammogram prior to initiating therapy.

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## Efficacy of SSRI antidepressants versus placebo

One in six people experience depression at some time in their life,<sup>1</sup> and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed as first line therapy to treat depression in the United States. Meta-analysis and recent review articles reported to the FDA indicate that SSRIs may be of no benefit over placebo in treating major depression. Mild depression can be treated with psychotherapy, but more severe depression often requires prescription medication such as tri-cyclic antidepressants (TCA,) monoamine oxidase inhibitors (MAO-I,) or SSRIs. It is important to further examine the benefit versus risk of using SSRIs over other antidepressants.

A meta-analysis of the clinical trial data reported to the FDA by drug manufacturers regarding severity of initial depression and the benefits of antidepressants has prompted recent concern whether SSRIs are of benefit over placebo in treating depression.<sup>1</sup> The analysis found that antidepressant medications had only modest benefit over placebo, and the relationship between initial severity of depression and antidepressant efficacy was not associated with a response to medication, but rather to a decreased response to placebo. Data on all clinical trials conducted for fluoxetine, venlafaxine, nefazodone, paroxetine, sertraline and citalopram were reviewed. The data set consisted of 35 clinical trials: (fluoxetine (5), venlafaxine (6), nefazodone (8) and paroxetine (16). There were 3,292 patients randomized to the medication groups and 1,841 randomized to the placebo groups, for a total of 5,133 patients. Results from the analysis were compared to the criteria for clinical significance used by the National Institute for Clinical Excellence (NICE). A three-point difference in Hamilton Rating Scale of Depression (HRSD) scores or a standardized mean difference of 0.50 were proved. Weighted mean improvement were 9.60 points on the HRSD scale for the treatment group and 7.80 in the placebo group, which gave an average drug-placebo difference of 1.80. This difference is statistically significant, but does not meet the three-point drug-placebo criteria for clinical significance used by NICE. In conclusion, SSRIs only modestly improve symptoms in major depression.



Choosing the most appropriate medication for a patient is difficult, and many patients may need to experiment with several SSRIs before they are placed on the most beneficial agent. A meta-analysis of comparative data of 6 SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and 4 other antidepressants (bupropion, duloxetine, mirtazapine, and venlafaxine) were reviewed.<sup>2</sup> Forty-six randomized, controlled trials compared the efficacy of one antidepressant with that of another agent in the treatment of major depression. Overall, the studies reported similar outcomes. The majority of trials reported no statistically significant differences in efficacy between the various classes of antidepressants. Small sample size may be the cause for statistical significance in some trials. The authors suggested that if a larger sample size were used in these trials, no statistical significant difference between the SSRIs would exist in treating major depression.

In summary, these systematic reviews found that there is no significant difference in efficacy when treating major depression between the various SSRIs, and further, there is only modest benefit for treatment of depression versus placebo. Benefits of using SSRIs for treatment of depression should be weighed against the risks of these medications prior to prescribing them.

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## Antiepileptic Medications Linked to Increased Risk of Suicide

On January 31, 2008 the Food and Drug Administration (FDA) issued new information about an increased risk of suicide in patients taking antiepileptic medications to treat epilepsy, bipolar disorder, migraines, and other conditions.<sup>1</sup> The FDA analyzed 199 placebo-controlled studies of 11 antiepileptic medications and determined that taking these medications significantly increased the risk of suicide. An estimated 2.1 per 100 (95% CI: 0.7, 4.2) more patients in the drug treatment group experienced suicidal behavior or ideation than in the placebo treatment groups (0.43% of patients taking an antiepileptic medication compared to 0.22% of patients taking placebo)<sup>2</sup>. The 11 antiepileptic medications analyzed were carbamazepine (Tegretol), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), valproate (Depakote), and zonisamide (Zonegran).

The 199 studies analyzed encompassed 27,863 patients in a drug treatment group and 16,029 patients in a placebo group.<sup>2</sup> The FDA reported that increased suicidal thoughts and behaviors were observed after 1 week of starting an antiepileptic medication and continued to at least 24 weeks, the longest time period any trial was conducted. Of the 199 studies analyzed, four patients taking an antiepileptic medication committed suicide, and no patients taking a placebo committed suicide. No differences in suicide risk were seen between medication groups. Also, no differences were found between different demographic subgroups or age groups. Significance data was not provided for these findings.

Based on these findings, the FDA is working to include warnings about increased risk of suicide in the labeling of all antiepileptic medications in the future, and intends to work with drug companies to change the labels of the drugs over the next several months to reflect this risk.<sup>3</sup>

Aside from the recent analysis by the FDA, there are limited studies with the primary endpoint of determining a change in incidence of suicidality with administration of antiepileptic agents. Two case reports have been written about individuals who became suicidal or attempted suicide after starting topiramate regimens. A 41 year old women with bipolar disorder developed suicidal symptoms a few weeks after her topiramate dose was gradually increased to 150 mg daily.<sup>4</sup> The topiramate was discontinued immediately and within one week she was symptom-free. A similar case report was written about a 72 year old male with no past or family history of mental illness, impulsivity, or suicidality of any kind.<sup>5</sup> Eight days after starting and titrating topiramate to 50 mg daily, he ingested a potentially lethal amount of ethylene glycol after an argument with his wife. His topiramate was discontinued and at his 4 week follow-up he denied any suicidal ideation.

The FDA feels that increased suicide risk is class-wide and not confined to the 11 antiepileptic medications studied.<sup>1</sup> The FDA suggests that all patients taking antiepileptic medications be monitored by a caregiver for warning signs that signal risk for suicide and for other unusual changes in behavior. Patients should be warned directly about the increased incidence of suicide. Patients should be urged not to make any changes to antiepileptic therapy without first consulting with a healthcare professional.

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## Wealthy and Insured More Likely to Receive Free Drug Samples, but May End Up Costing More in the End

In February 2008, the Agency for Healthcare Research and Quality's 2003 Medical Expenditure Panel Survey (MEPS), Household Component, reported that Americans with a higher income, and those covered by insurance, were more likely to receive free drug samples than those who were poor and uninsured. The MEPS performed a nationally representative longitudinal survey of the civilian non-institutionalized U.S. population. Information was collected on health care expenditures, health care utilization, health insurance, and socio-demographic characteristics, as well as information on all outpatient medications used by each family member. The use of free prescription drug samples provided by health care professionals was also recorded.

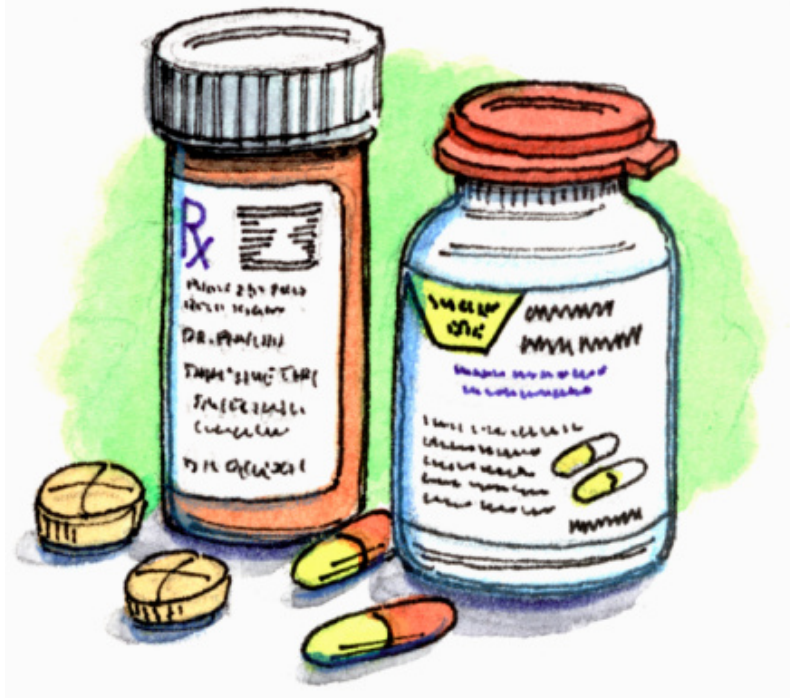


Three questions were investigated: 1) Are free drug samples more frequently given to uninsured and low-income persons than those who are insured and more affluent? 2) Did the type of drug coverage influence the likelihood of receiving free samples? And 3) Which drugs are most commonly distributed as samples? The analysis found that free drug samples were given to 12% of the US population. Of those recipients, less than one-fifth were uninsured at any point during the year and less than one-third were considered low income. Of the subjects uninsured for all or part of the year, 9.9% received free drug samples, compared to 12.9% of insured subjects ( $p < 0.001$ ). When assessing income, 72% of those who received samples had an income in excess of 200% above poverty level. Respondents who received medical care in a hospital emergency department (10%) or had no usual source of medical care (6.3%) were less likely to receive samples than those who received medical care in a physician's office (14.3%,  $p < 0.001$ ). Overall, it was found that the wealthy and insured were more likely to be given free drug samples. The authors concluded that free drug samples serve as a manufacturer's marketing tool rather than as a safety net for the underprivileged.

In April 2008, another report based on the 2003 MEPS claimed that patients receiving free drug samples spend more out-of-pocket on prescription costs than those who do not receive samples. Before ever receiving a sample, subjects' average out-of-pocket prescription costs were similar to those who never received samples. However, after receiving samples, subject's out-of-pocket prescription costs were on average \$66 more than those who never received samples (\$244 vs. \$178;  $p < 0.001$ ). It may be that individuals receiving samples are more likely to continue taking the same sample medication rather switching to a cheaper alternative, or to no medication at all. Patients receiving free drug samples could be sicker and therefore require prescription drugs for a longer period of time. The authors concluded that higher prescription expenditures are seen in individuals who receive samples compared to those who do not. Based on this study, receiving free samples increases financial burden in the long run.

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