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Protecting and Promoting Public Health

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IN THIS ISSUE

THE NEWSLETTER'S MISSION

This publication provides postmarketing information to healthcare professionals to enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting. For more information, visit the FDA Drug Safety Newsletter Fact Sheet at *www.fda.gov/cder/dsn/factsheet.htm*.

REPORTING ADVERSE EVENTS

FDA encourages the reporting of all suspected adverse drug reactions, drug interactions, and reactions that result in death, life-threatening outcomes, hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defects.

Report serious adverse events to FDA's MedWatch reporting system by completing an online form at *www.fda.gov/medwatch/report.htm*, by faxing (1-800-FDA-0178), by mail using the pre-paid postage address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

EDITOR'S NOTE

As we begin the second year of FDA's Drug Safety Newsletter, we continue to inform healthcare professionals on the findings of selected and important postmarket drug safety reviews, emerging and continuing drug safety issues, and recently approved new molecular entities. We also continue to provide our readership with a quarterly list of FDA's drug safety communications.

In this issue, we describe our analysis of suicidal ideation and behavior associated with the use of smoking cessation aids. FDA has received reports of suicide-related events in patients attempting to break their nicotine habit with the aid of varenicline (Chantix) or bupropion (Zyban and generics). These events occurred in people with and without preexisting psychiatric conditions.

In another article, we present a summary of postmarket data on abacavir (Ziagen) and abacavir–containing products (Epzicom and Trizivir) and a hypersensitivity reaction known to occur with this drug. Specifically, we describe the use of HLA-B*5701 screening in identifying patients susceptible to this reaction, as well as address the issue of skin patch testing. The use of abacavir skin path testing to rechallenge patients has not been validated and should not be used in clinical practice.

We also describe the occurrence serious liver injury in adults and children who use the drug atomoxetine (Strattera). This drug is the first non-stimulant drug in the United States indicated for the treatment of ADHD.

Finally, this issue of Drug Safety Newsletter presents a brief description of FDA's Patient Safety News, a monthly video series produced by FDA. We encourage health care professionals to watch, download, and distribute this video – free of charge – at *www.fda.gov/psn*.

We continue to value your feedback. Please submit your comments to us at *www.fda.gov/cder/comment.htm*. Healthcare professionals are reminded to report serious adverse events to FDA at *www.fda.gov/medwatch/report.htm*.

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Sr. Scientific Editor

POSTMARKET REVIEWS

THE SMOKING CESSATION AIDS VARENICLINE (MARKETED AS CHANTIX) AND BUPROPION (MARKETED AS ZYBAN AND GENERICS)

Suicidal Ideation and Behavior

Abstract: An analysis of Adverse Event Reporting System (AERS) reports identified cases of suicidality associated with the use of varenicline and bupropion, two products used as smoking cessation aids. This report provides FDA's summary analysis of these cases.

Keywords: varenicline, bupropion, nicotine, suicide

A postmarket safety review of varenicline (marketed as Chantix) and bupropion (marketed as Zyban and generics), two products used for smoking cessation, has identified cases where suicidal ideation and behaviors followed the initiation of treatment with these drugs. Although this review also evaluated transdermal nicotine products (marketed as Habitrol, Nicoderm, Nicoderm CQ, and Prostep), no clear association was identified between the use of these products and suicidal ideation and/or behavior (these data have not been included in this report).

For both varenicline and bupropion, cases of suicidality were reported among patients with and without a prior psychiatric history. Healthcare professionals should continue to closely monitor patients treated with these drugs for neuropsychiatric symptoms (e.g., changes in behavior, agitation, depressed mood, and suicidal thoughts and behavior), as directed in the *Warnings* section of varenicline label and the *Boxed Warning, Warnings and Precautions* section of the bupropion label.[1,2]

In 2006, varenicline (0.5 and 1 mg tablets) was

approved for use as a pharmacological aid for smoking cessation. Varenicline is a high affinity, partial agonist at the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype. Its competitive binding with nicotine and partial agonist activity at the $\alpha_4\beta_2$ receptor are believed to be responsible for this drug's therapeutic effect.[3,4]

Bupropion was first approved in 1985 for the treatment of Major Depressive Disorder. Buproprion 150 mg extended release tablet (Zyban) was approved for the smoking cessation indication in 1997. In the following years, generic forms of this drug became available for smoking cessation treatment. Bupropion is a monocyclic aminoketone antidepressant chemically unrelated to the more traditional tricyclic, tetracyclic or SSRI antidepressants. It is a relatively weak inhibitor of the neuronal norepinephrine and dopamine, and does not inhibit monoamine oxidase or alter the re-uptake of serotonin. Although the mechanism by which bupropion produces its therapeutic effect is unknown, it is generally assumed that its action on noradrenergic and/or dopaminergic activity contributes to the drug's efficacy.[5]

FDA reviewed AERS cases describing suicidal ideation† and behavior†† reported for these compounds from the date of each compound's approval (from approval of the smoking cessation indication for bupropion) to November 27, 2007. FDA identified 153 reports of suicidal adverse events for varenicline (suicidal ideation-116, suicide-37) and 75 reports for bupropion (suicidal ideation-46, suicide-29). These cases likely represent a fraction of those that occurred during this time period due to underreporting to FDA's Adverse Event Reporting System (AERS). The total yearly prescriptions and units sold for these products is estimated in the millions. The data summarized below represent these AERS cases.

REPORTED CASES OF SUICIDAL IDEATION AND BEHAVIOR

The demographic data of these AERS cases, if provided, are listed in Table 1. When evaluating the temporal relationship between the initiation of treatment and the time-to-onset for these adverse suicidal events, a large percentage of AERS reports indicated that suicidal ideation and behavior occurred while the individual was undergoing treatment for smoking cessation. For varenicline, out of the 128 cases that reported time-to-onset, 86% reported that symptoms began while taking the drug. Of the 72 bupropion cases reporting time-to-onset, 93% noted an onset of suicidal ideation and behavior while the patient was taking the drug. For both drugs, the median time to event onset was less than two weeks. A similar proportion of cases for varenicline (35%) and bupropion (33%) reported symptom abatement after discontinuation of the drug.

Complementing these data, 41% of varenicline cases (63/153 cases reporting) reported that the change in thinking or behavior was a *significant change* from the past. In 37 of these 63 cases (59%), this was a first time experience, while the remaining 26 cases noted there was a worsening of pre-existing psychiatric disease (which the reporter had previously felt was stable). A similar pattern was seen with bupropion. Twenty-three percent of cases (17/75 cases reporting) stated a *significant change* from the past in thinking and/or behavior occurred after initiating treatment. In 11 of these 17 cases (65%), this was a first time experience. The remaining six cases noted there was a worsening of pre-existing, yet stable, psychiatric condition.

For those reports indicating drug dose, most individuals, independent of the type of treatment or whether they experienced suicidal ideation or behavior, were taking the drug at the recommended dose. Specifically, 95% of varenicline reports indicating suicidal ideation (78/82) and 93% of varenicline reports indicating suicidal behavior (15/16) noted that the patient was taking the recommended dose. For bupropion, 96% of reports indicating suicidal ideation (25/26) and 100% of bupropion reports indicating suicidal behavior (14/14) noted that the patient was taking the recommended dose.

Table 1. Selected demographics of AERS reports of suicidal ideation (SI) and suicidal behavior (SB) with varenicline and bupropion

Demographics	Varenicline		Bupropion	
	SI	SB	SI	SB
Age in Years (cases reporting)	**n=106**	**n=27**	**n=33**	**n=24**
Median	44.5	46.3	46	35
Range	20-83	22-72	26-70	15-70
Sex (cases reporting)	**n=115**	**n=34**	**n=43**	**n=29**
Male	26%	50%	40%	59%
Female	74%	50%	60%	41%

The psychiatric variables associated with the varenicline and bupropion reports of suicidal ideation and behavior are listed in Table 2. For varenicline cases, approximately half indicated that the suicidal events occurred in patients with psychiatric histories. Forty-two percent of cases also noted that the patient was currently taking psychotropic medications in addition to the smoking cessation aid at the time of the event. A smaller percentage of cases reported these concurrent factors in bupropion-treated patients. It is important to note that many of the patients who reported suicidality did not have a psychiatric history and/or were not taking psychotropic medications. In addition, there were many cases that did not provide information on psychiatric history or concomitant psychotropic medications.

For both compounds, a psychiatric history of depression was frequently reported. Specifically, of the 77 varenicline reports indicating the patient had a psychiatric history, 58% (45/77) reported a history of depression. Of the 18 bupropion reports indicating the patient had a psychiatric history, 66% (12/18) reported a history of depression. Depression was also frequently reported as a co-occurring psychiatric event at the time of reporting. Specifically, 50%, and 70% of varenicline and bupropion reports, respectively, had depression listed as a co-occurring psychiatric event.

Table 3 lists the outcomes associated with the varenicline and bupropion suicidal ideation and behavior reports. The majority of outcomes were serious and included, although not mutually exclusively from, death and

Table 2. Psychiatric variables noted in AERS reports of suicidal ideation (SI) and suicidal behavior (SB) with varenicline and bupropion. The variables of Psychiatric History and Concomitant Psychiatric Medications are not mutually exclusive.

Psychiatric Variables	Varenicline			Bupropion		
	SI	SB	Total	SI	SB	Total
Total Cases	**n=116**	**n=37**	**n=153**	**n=46**	**n=29**	**n=75**
Psych History	54%	38%	50%	26%	21%	24%
No Psych History	25%	30%	26%	35%	27%	32%
Unknown Psych History	21%	32%	24%	39%	52%	44%
Concomitant Psych Meds	42%	30%	39%	20%	17%	19%
No Concomitant Psych Meds	20%	24%	21%	41%	21%	33%
Unknown Concomitant Psych Meds	38%	46%	40%	39%	62%	48%

Table 3. Outcomes noted in AERS reports of suicidal ideation (SI) and suicidal behavior (SB) with varenicline and bupropion. The outcomes listed below are not mutually exclusive.

Outcomes	Varenicline			Bupropion		
	SI	SB	Total	SI	SB	Total
Serious (cases reporting)	**n=110**	**n=37**	**n=147**	**n=30**	**n=29**	**n=59**
Death	0%	51%	13%	0%	34%	17%
Hospitalization	11%	19%	13%	30%	41%	36%
Life-Threatening	24%	14%	21%	33%	21%	27%
Disability	5%	8%	6%	10%	7%	8%
Required Intervention	5%	0%	4%	3%	3%	3%
Other	84%	54%	76%	37%	24%	31%
Non-Serious (cases reporting)	**n=6**	**n=0**	**n=6**	**n=16**	**n=0**	**n=16**

BOX 1

Varenicline

Case 1

A 45 year-old female nurse reported she was taking varenicline, as directed, to aid in the cessation of smoking. She had been a smoker (1-1.5 packs/day) for approximately 4 years. After 10 weeks of varenicline treatment, she reported she was experiencing suicidal ideation, aggression, erratic behavior, uncontrollable emotions, and decreased clarity. One week after discontinuing varenicline, she reported that [her symptoms] were "not at the levels listed above," although she still experienced some "residuals." She described her alcohol use as rare and reported treatment for hypothyroidism with Synthroid.

Case 2

A 30 year-old female reported that she was taking varenicline 0.5 mg/day to help her quit smoking. She indicated that she had taken the pill for 5 days as directed. In her report, she stated, "I became very depressed for no apparent reason and started having suicidal thoughts. I worried that I was going to hurt myself or someone else. I was also in a state of panic and unable to eat. I thought that I might go crazy and felt completely out of sorts. I quit taking the pill. About 36 hours later, I felt like myself again."

Bupropion

Case 3

A 27 year-old female with a history of smoking 1 pack/day for the past 11 years was taking bupropion 150 mg BID as a smoking cessation aid. Fifteen days into bupropion treatment, the patient reported feeling "emotional" and was having regular crying fits. The patient threatened to kill herself and stated, "I didn't care if I lived." The patient had no documented history of depression.

Case 4

A 46 year old male smoker was taking bupropion 150 mg BID for four days when he experienced depression, panic, paranoia, sensory changes and thoughts of suicide. The patient discontinued his medication at that time. No other information on the resolution of this event was provided. The patient reported that he had a family history of chronic depression.

hospitalization. Four cases describing an adverse suicidal event while patients were taking varenicline or bupropion are presented in Box 1.

Together, the AERS data suggest a possible association between suicidal events and the use of varenicline and bupropion. Healthcare providers are reminded to closely monitor patients for neuropsychiatric symptoms (e.g., changes in behavior, agitation, depressed mood, and suicidal thoughts and behavior) while they are using varenicline and bupropion as smoking cessation aids. Healthcare providers should report any cases of suicidal ideation and/or behavior in patients taking these drugs to FDA's MedWatch program at *www.fda.gov/medwatch/*. Given the well-established health risks of smoking, healthcare providers should continue to work closely with patients to assist them in quitting smoking. FDA

RELEVANT WEBSITES

National Institute on Drug Abuse website on nicotine
http://drugabuse.gov/DrugPages/Nicotine.html

Centers for Disease Control and Prevention website on smoking and tobacco
www.cdc.gov/tobacco/index.htm

Public Health Advisory on varenicline
www.fda.gov/cder/drug/advisory/varenicline.htm

FOOTNOTES:

† Suicidal ideation included the search terms 'suicidal ideation', 'self-injurious ideation', 'suicidal depression'.

†† Suicidal behavior included the search terms 'completed suicide', 'attempted suicide', 'intentional self-injury', 'self-injurious behavior', 'suicidal behavior', 'multiple drug overdose', 'gun shot wound', 'intentional misuse', and 'overdose'

REFERENCES

1. Varenicline (Chantix) Product Labeling
   www.fda.gov/cder/foi/label/2008/021928s008lbl.pdf
2. Bupropion (Zyban) Product Labeling
   www.fda.gov/cder/foi/label/2007/020711s029lbl.pdf
3. Stack NM. Smoking cessation: an overview of treatment options with a focus on varenicline. Pharmacotherapy. 2007;27(11):1550-7.
4. Potts LA, Garwood CL. Varenicline: the newest agent for smoking cessation. Am J Health Syst Pharm. 2007;64(13):1381-4.
5. Jorenby D. Clinical efficacy of bupropion in the management of smoking cessation. Drugs. 2002;62(Suppl 2):25-35.

Quitting smoking reduces the risk of cardiovascular disease, pulmonary disease, and cancer

ABACAVIR (MARKETED AS ZIAGEN) AND ABACAVIR-COMBINATION PRODUCTS (MARKETED AS TRIZIVIR AND EPZICOM)

Hypersensitivity reaction, HLA-B*5701, and skin patch testing

Abstract: As of July 2008, the *Boxed Warning* of the abacavir product labeling recommends that patients be screened for the human leukocyte allele, HLA-B*5701, prior to initiating abacavir treatment. Screening patients for HLA-B*5701 reduces the risk for an abacavir (ABC) hypersensitivity reaction (HSR). If an ABC HSR is suspected, healthcare professionals are directed to discontinue ABC immediately and not rechallenge patients with this drug. Although the abacavir skin patch test (research use) may appear to be be a simple solution to aid in the diagnosis of an ABC HSR, a clinical syndrome with a degree of diagnostic uncertainty, the predictive value of skin patch testing is not fully understood. The use of skin patch testing is difficult to justify as the basis for rechallenging a patient with ABC, given the risk for a fatal systemic reaction.

Keywords: abacavir, hypersensitivity reaction, HLA-B*5701, skin patch testing

Abacavir (ABC) sulfate (Ziagen; also in the combination products Trizivir and Epzicom), a nucleoside reverse transcriptase inhibitor indicated for treatment of HIV-1 infection, has been associated with a unique, serious, and sometimes fatal hypersensitivity reaction (HSR). ABC HSR is a multi-organ syndrome which typically occurs within six weeks of initiating ABC treatment.[1] The most common symptoms of an ABC HSR include fever (~80% of cases), rash (~70% of cases), malaise/fatigue, nausea, and vomiting. Other signs and symptoms of an ABC HSR may include myalgia or arthralgia, headache, diarrhea, pruritis, hypotension, and various respiratory symptoms. Development of an ABC HSR requires immediate and permanent discontinuation of the drug, as rechallenge can be fatal.[2]

Correctly diagnosing an ABC HSR is critical given the severe consequences of this reaction to the patient and the utility of this drug in managing HIV. Unfortunately, the diagnosis of an ABC HSR can be difficult. An ABC HSR may mimic common infections, or may be confused with adverse events seen with other concomitant or prophylactic medications used for the treatment of HIV, or with opportunistic infections commonly seen in patients with HIV. A review of literature indicates that misdiagnosis of an ABC HSR can occur in approximately two to seven percent of patients, independent of whether patients are even taking ABC.[1,3]

One risk factor that has been shown to be associated with the development of an ABC HSR is the presence of the human leukocyte allele, HLA-B*5701.[4,5] In one prospective, randomized clinical trial (PREDICT-1), not treating patients positive for HLA-B*5701 with abacavir significantly reduced the incidence of clinically suspected cases of an ABC HSR from 7.8% to 3.4%.[6] Data from this study suggest that 61% of HLA-B*5701 positive subjects may develop an abacavir HSR during the course of therapy compared with 4.5% of HLA-B*5701 negative subjects. As of July 2008, the *Boxed Warning* on the abacavir product labeling recommends that patients be screened for HLA-B*5701 prior to initiating abacavir treatment.[6]

Even with genetic screening for HLA-B*5701, and refraining from initiating abacavir treatment in those patients positive for this allele, some patients may develop an ABC HSR. As noted above, HLA-B*5701 is not 100% predictive of an ABC HSR. Some patients negative

Table 1. This table lists the systems and signs and symptoms involved in the "≥ 2 signs and symptoms from 2 systems" rule used in the clinical diagnosis of ABC HSR.

System	Signs and Symptoms
Group 1	Fever
Group 2	Rash
Group 3	Nausea, Vomiting, Diarrhea, Abdominal Pain
Group 4	Malaise, Tiredness, Myalgias or Arthralgias
Group 5	Shortness of Breath, Cough, Sore Throat

for this allele may still develop signs and symptoms suggestive of an ABC HSR. For this reason, healthcare professionals should closely monitor patients taking abacavir for potential signs and symptoms of this reaction (see Table 1).

If an ABC HSR is suspected, healthcare professionals are directed to discontinue ABC immediately and not rechallenge patients with the drug or by any other means.

Several research reports have emerged that have used skin patch testing to immunologically confirm suspected cases of an ABC HSR.[7,8] Specifically, in an analysis of race differences in ABC HSRs among black and white subjects positive for HLA-B*5701, white HLA-B*5701 positive subjects with a HSR were more likely to be skin patch test positive than black HLA-B*5701 positive subjects with a HSR.[8] Among the 10 HLA-B*5701 positive black subjects, 5 were skin patch test positive and 5 were skin patch test negative. These data suggest that skin patch testing was not predictive for an ABC HSR in patients positive for the HLA-B*5701 allele. Conversely, only 32.3% (42/130) of white and 7.2% (5/69) of black patients who were skin patch tested and who met criteria for clinically suspected ABC HSR had a positive skin patch test for an ABC HSR. Healthcare professionals must be aware that the use of skin patch testing to immunologically confirm cases of an ABC HSR remains in the realm of research and that skin patch testing has not been clinically validated. Skin patch testing may miss cases of true ABC HSR or provide false positive results. The accuracy of skin patch testing results is unknown in a broad population.

Given the risks associated with rechallenging patients with ABC when a HSR is suspected, that is, an increased risk of mortality, the diagnosis of ABC HSR must remain a clinical one in all patients (see Table 1). Although skin patch testing appears to be a simple solution to aid in the diagnosis of a clinical syndrome with diagnostic uncertainty, the positive and negative predictive value of the abacavir skin patch test are not fully understood, making its use to justify a potentially fatal systemic abacavir rechallenge a risky endeavor. FDA

RELEVANT WEBSITES

Information sheet on Abacavir and Abacavir – containing medications: *www.fda.gov/cder/drug/InfoSheets/HCP/abacavirHCP.htm*

Abacavir (Ziagen) product labeling
www.fda.gov/cder/foi/label/2008/020977s017,020978s020lbl.pdf

Abacavir sulfate; lamivudine (Epzicom) product labeling
www.fda.gov/cder/foi/label/2007/021652s005lbl.pdf

Abacavir sulfate; lamivudine ; zidovudine (Trizivir) product labeling
www.fda.gov/cder/foi/label/2007/021205s018lbl.pdf

Medication Guide for Abacavir products:
www.fda.gov/cder/Offices/ODS/MG/abacavirMG.pdf

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents:
www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

REFERENCES:

1. Shear NH, Milpied B, Bruynzeel DP, Phillips EJ. A review of drug patch testing and implications for HIV clinicians. AIDS. 2008;22(9):999-1007.
2. Escaut L, Liotier JY, Albengres E, et al. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. AIDS. 1999;13(11):1419-20.
3. Hernandez J, Cutrell A, Bonny T, et al. Diagnosis of abacavir hypersensitivity reactions among patients not receiving abacavir in two blinded studies. Antivir Ther. 2003;8:L88.
4. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359(9308):727-32.
5. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359(9312):1121-2.
6. Abacavir product labeling. *www.fda.gov/cder/foi/label/2008/020977s017,020978s020lbl.pdf*
7. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358:568–79.
8. Saag M, Balu R, Phillips E, et al. High sensitivity of Human Leukocyte Antigen-B*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis. 2008;46:1111-18.

REMINDER: HOW TO REPORT ADVERSE REACTIONS

Report serious adverse events to FDA's MedWatch reporting system by completing an online form at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178), by mail using the pre-paid postage address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

ATOMOXETINE (MARKETED AS STRATTERA)

Serious liver injury

Abstract: In 2004, the atomoxetine label was updated to include information about cases of serious liver injury. From January 2005 to March 2008, six postmarket cases of serious liver injury with atomoxetine use were reported to FDA. None of the patients that developed serious liver injury had liver transplants. One patient with serious liver injury died, although it is unclear if atomoxetine caused or contributed to this event. Patients and caregivers should be alert to the signs and symptoms of liver injury throughout atomoxetine treatment. Atomoxetine should be discontinued and not resumed if a patient presents with jaundice or laboratory evidence of hepatotoxicity.

Keywords: atomoxetine, hepatotoxicity, ADHD

FDA continues to receive reports of serious liver injury in patients given atomoxetine. Atomoxetine received FDA approval on November 26, 2002 as the first non-stimulant medication used for the treatment of attention deficit hyperactivity disorder (ADHD) in children (ages 6 years and above) and adults.[1] Atomoxetine's therapeutic action is believed to be due to its selective inhibition of norepinephrine reuptake. From the year 2002 to 2007, approximately 3.3 million patients received a prescription for atomoxetine in the United States. Of those, approximately 2.1 million patients (64%) were children ages 17 years and younger.[2]

While a signal for serious liver injury was not detected during premarket clinical trials of atomoxetine, two published postmarket reports did identify instances of atomoxetine-induced hepatitis.[3,4] In one of these reports, there was a positive rechallenge with atomoxetine. Subsequent to these reports, a bolded warning was added in 2004 to the atomoxetine label indicating an increased risk for severe liver injury.

Since the 2004 labeling change, FDA received six additional reports of serious liver injury in patients taking atomoxetine. Following an evaluation of the information from the drug sponsor and additional literature articles submitted to FDA, the atomoxetine product label was again revised in 2007. The *Warnings* and *Precautions* section of the drug label advises prescribers about the risk for severe liver injury with this drug.[1] Healthcare professionals and patients should be watchful for serious liver injury associated with the use of atomoxetine and report cases to FDA's MedWatch.

The following paragraphs summarize FDA's analysis of these six Adverse Event Reporting System (AERS) cases of atomoxetine-associated liver injury. These reports were received between January 2005 and March 19, 2008. Two of the six cases are described in the medical literature.[3,4,5]

Table 1 summarizes some of the characteristics of these cases. Five of the six cases were among patients 17 years of age and younger.

BOX 1

What is drug-induced liver injury?

The liver is the main organ for metabolizing, activating and/or deactivating drugs prior to excretion via the bile or urine. Sometimes the drug (or its metabolites) can cause chemical injury to liver cells. This injury can vary in severity from asymptomatic elevations of blood enzyme activities to liver failure and a need for transplantation. This injury can also result in death. Drug-induced liver injury (DILI) is now the most frequent cause for acute liver failure in the United States, exceeding all other causes (e.g., viral, alcoholic, autoimmune, ischemic) combined. It is also one of the main reasons for not approving new drugs, or for removing drugs from the market after they were approved for clinical use.

The mechanisms causing DILI are not well understood. There are several ways the injury can present in patients including jaundice, nausea and vomiting, abdominal pain, bleeding, mental confusion, and/or kidney failure. Although exceedingly rare for most drugs, almost any drug can cause DILI. Still, some drugs are more likely than others to result in this injury. The main determinant for DILI may be individual differences in constitution or manner of responding to the drug. That is, some patients may be more sensitive than others to DILI. Injuries due to individual differences are generally called "idiosyncratic reactions." Severe idiosyncratic reactions, while generally rare, may occur at much lower doses than those that are well-tolerated and handled by most people.

The FDA, along with partners in academia and industry, is engaged in research into questions about DILI and sponsors an annual public conference on this topic. The proceedings from the conference can be found at *www.fda.gov/cder/livertox*.

In four cases, the patients presented with jaundice and one or more symptoms, including fatigue, lack of appetite, abdominal pain, nausea, or vomiting. Acute impairment of liver function, as manifested by the inability to synthesize sufficient prothrombin (PT) to produce a normal INR or the inability to clear bilirubin, was observed at the time of diagnosis in three of the six patients. Two patients had significant increases in hepatic enzymes. In one case, profiled in Box 2, peak AST and ALT levels were 6619 IU/L [73 x upper limit of normal (ULN)] and 5182 IU/L (86 x ULN), respectively; peak total bilirubin (TB) was 14.7 mg/dl. Viral titers for hepatitis A, B, and C, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) IgM were negative in two cases with elevated hepatic enzymes. Liver biopsies showed hepatic inflammation/fibrosis in one patient and inflammation with moderate piecemeal necrosis in the other.

Although the majority of patients were hospitalized, none required a liver transplant. Four patients recovered after atomoxetine was discontinued. One adult, male patient died due to hepatic and renal failure. Because there were limited details available about this case, the role of atomoxetine in this patient's death could not be determined. Over the course of two years, this patient had alternated atomoxetine 80 mg/day with methylphenidate in order to manage his ADHD.

Three patients in this case series reported a history of occasional acetaminophen use, the use of a recent, single dose of mebendazole, or concomitant quetiapine use. None of these drugs were felt to have contributed to the liver injury.

Two representative cases illustrating the relationship between atomoxetine and serious liver injury are summarized in Box 2. The cases were selected based on a temporal relationship between initiation of atomoxetine and onset of symptoms indicative of a liver injury. Both patients presented with elevated hepatic enzymes and jaundice, and had extensive clinical work-ups, including liver biopsies and tests to rule out non-drug causes of liver injury. Both patients recovered upon atomoxetine discontinuation. The two cases are also described in the medical literature.[3,4,5]

Postmarket reports indicate that atomoxetine is associated with serious idiosyncratic liver injury. Some of the cases reported additional confounding factors, such as occasional acetaminophen use. Some of the cases lacked sufficient clinical detail to convincingly detail the relationship between the use of atomoxetine and liver injury. The mechanism of atomoxetine-induced liver injury remains unknown. FDA continues to monitor AERS for reports of serious liver injury in association with atomoxetine.

FDA encourages physicians to:

- Inform patients to immediately contact their physician at the first sign or symptom of fatigue, loss of appetite, nausea, vomiting, pruritis, dark urine, jaundice of the sclerae or skin, right upper quadrant tenderness, or unexplained "flu–like" symptoms

Table 1. Characteristics of the six cases of atomoxetine-associated severe liver injury

Age (years)		Time to onset (days)	
Median	10.5	Median	62.5
Range	6-26	Range	21-730
Sex		**Reports**	
Male	n=4	U.S.	n=5
Female	n=2	Non-U.S.	n=1
Dose (n=4)		**Serious Outcome**	
Median	32.5 mg	Hospitalization	n=5
Range	10-80 mg	Death	n=1

BOX 2

Case 1

A 12-year-old female diagnosed with ADHD experienced jaundice and elevation of liver enzymes when she restarted atomoxetine 40 mg daily following a 6-week interruption of a year-long therapy. This patient had no history of liver disease, or exposure to hepatitis or any known hepatotoxins. Three weeks after restarting atomoxetine, she was hospitalized for jaundice, abdominal pain, diarrhea, and vomiting. Upon admission, she had stable vital signs, conjunctival icterus, and tenderness in her right upper quadrant. She had no hepatosplenomegaly. She was evaluated for acute hepatitis.

Over the course of the event, her peak liver biomarkers were AST: 3505 U/L (78 x ULN), ALT: 3264 U/L (65 x ULN), TB: 9.8 mg/dL (~10 x ULN), GGT: 108 U/L (normal reference range: 12-43), and PT: 14.1 seconds (normal reference range: 10.8–13.7). Her serum alkaline phosphatase (AP) was normal. A liver biopsy confirmed hepatic inflammation and fibrosis. Testing for hepatitis A, B, C, CMV, and EBV were negative. An antinuclear antibody (ANA) titer was positive (1:160; normal reference range: < 1:40). Smooth muscle antibodies were negative, ceruloplasmin and alpha-1 antitrypsin were normal. The diagnosis of *drug-induced liver injury by atomoxetine* was made. Atomoxetine was discontinued. Four weeks later, she had an AST of 800 U/L, ALT of 1438 U/L, and TB of 2.6 mg/dL. Serum transaminase and bilirubin levels returned to normal approximately 6 months after discontinuation of atomoxetine.

see Case 2 next page ...

Case 2

An 8-year-old female with ADHD was being treated with atomoxetine 25 mg/day and developed vomiting, abdominal pain, jaundice, and very high serum aminotransferases approximately five weeks after starting therapy. She was hospitalized and atomoxetine was discontinued. She had no known history of liver disease. The child occasionally received therapeutic doses of acetaminophen from a parent (~10 times/month) for soccer-related musculoskeletal pains. She also received one dose of mebendazole for a pinworm infection nine days after starting atomoxetine therapy. Upon admission to the hospital, her physical exam was significant for scleral icterus, jaundice, and hepatomegaly. The peak values of liver markers were AST: 6619 U/L (73 x ULN), ALT: 5182 U/L (86 x ULN), TB: 14.7 mg/dL (~14 x ULN), AP: 528 U/L (3.5 x ULN), and GGPT: 196 U/L (2.5 x ULN). Testing for hepatitis A, B, C, CMV, and EBV were negative. An abdominal ultrasound showed mild hepatomegaly with no gallstones or ductal dilatation. Liver biopsy showed mixed portal inflammation and moderate piecemeal necrosis. Infectious, autoimmune and metabolic causes of liver injury were ruled out. No serum acetaminophen was detected. She received vitamin K, diphenhydramine, ursodiol, and fresh frozen plasma. The patient's transaminases and bilirubin serum levels began to improve approximately 13 days into her hospitalization. Within two months of her hospital discharge, her AST and ALT serum levels had decreased to 276 U/L (normal reference range: 25-45) and 178 U/L (normal reference range: 0-50), respectively.

- Determine liver enzyme levels when a patient presents with signs or symptoms of liver injury
- Discontinue and not resume atomoxetine treatment if patients present with jaundice or laboratory evidence of liver injury
- Report cases of serious liver injury to FDA's MedWatch program (*www.fda.gov/medwatch/*)

REFERENCES

1. Atomoxetine (Strattera) product labeling *www.fda.gov/cder/foi/label/2008/021411s024s025s026lbl.pdf*
2. Verispan Vector One®: National, Total Patient Tracker (TPT), 2002-2007, data extracted Sept 2007.
3. Bangs ME, Ling J, Zhang S, et al. Hepatic events associated with atomoxetine treatment for attention deficit hyperactivity disorder. Drug Safety. 2008;31(4):345-54.
4. Stojanovski SD, Casavant MJ, Hayat MM. et al. Atomoxetine-induced hepatitis in a child. Clin Toxicol (Phila). 2007;45(1):51-5.
5. Lim JR, Faught PR, Chalasani NP. Severe liver injury after initiating therapy with atomoxetine in two children. J Pediatr. 2006;148(6):831-4.

The FDA Patient Safety News Team

FDA Patient Safety News

One way healthcare professionals can receive additional information on the safety of new drugs, biologics, and medical devices, including product recalls, is by watching *FDA Patient Safety News*, a monthly video series produced by FDA. *FDA Patient Safety News* is broadcast over several medical satellite television networks aimed at hospitals and other medical facilities across the country. The video feature of *FDA Patient Safety News* allows patient protection techniques to be vividly demonstrated. This can be especially important when illustrating how medical errors occur, showing recalled products, teaching viewers to identify counterfeit products, and demonstrating how to reduce patient risks. Recent highlights from this broadcast include segments on serious fungal infections with Humira, Cimzia, Enbrel and Remicade, the importance of the influenza vaccination for healthcare personnel, and reported medication errors with oral opiate solutions. Even if your facility does not have access to *FDA Patient Safety News* broadcasts via a television network, we encourage healthcare professionals to watch, download or distribute these broadcasts free of charge at *www.fda.gov/psn*.

DRUG SAFETY COMMUNICATIONS

Drug Safety Communications posted by FDA from September 1, 2008 to November 30, 2008 (advisories are available at www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm)

Date	Product(s)	Safety Issue and Web Address
November 24, 2008	Phenytoin (Dilantin, Phenytek, and generics) and Fosphenytoin Sodium (Cerebyx and generics)	New data suggest a potential increased risk of phenytoin or fosphenytoin-induced serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) in patients with the human leukocyte antigen allele, HLA-B*1502. *www.fda.gov/cder/drug/InfoSheets/HCP/phenytoin_fosphenytoinHCP.htm*
November 12, 2008	Bisphosphonates [alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel with Calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa)]	Update to FDA's review of safety data regarding the potential increased risk of atrial fibrillation in patients treated with a bisphosphonate drug. One large study of zoledronic acid showed a statistically significant increase in the rate of serious atrial fibrillation events. However, across all studies involving 19,687 patients treated with bisphosphonates, no clear association between bisphosphonate use and serious or non-serious atrial fibrillation was observed. *www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm*
October 7, 2008	Tiotropium bromide (Spiriva HandiHaler)[1]	Ongoing safety review to evaluate increased risk of stroke in patients taking tiotropium bromide. Preliminary findings from the UPLIFT trial showed that there was no increased risk of stroke with the drug in comparison to placebo. *www.fda.gov/cder/drug/early_comm/tiotropium.htm*
September 26, 2008	Epoetin alfa [Eprex (not marketed in the US)][1]	Ongoing safety review to evaluate increased mortality in patients receiving epoetin alfa in a German clinical trial which studied the functional outcomes of patients after an acute ischemic stroke. Eprex is a member of the class of erythropoiesis stimulating agents (ESAs) that are approved by FDA for use in the treatment of anemia in certain patients. In a clinical trial involving 522 adult patients with a middle cerebral artery distribution ischemic stroke, there were more deaths in the epoetin alfa arm vs. the placebo arm (16% vs. 9%) over the first ninety days after the start of the trial. *www.fda.gov/cder/drug/early_comm/epoetin_alfa.htm*
September 4, 2008	Tumor Necrosis Factor (TNF) Blockers [infliximab (Remicade), etanercept (Enbrel), adalimimab (Humira), and certolizumab (Cimzia)]	Alert informing healthcare professionals about the risk of histoplasmosis and other invasive fungal infections in patients taking TNF blockers. These infections are not consistently recognized which may lead to delays in treatment and, in some cases, fatalities. FDA has asked manufacturers of each drug to highlight the risk in the *Boxed Warning* and *Warnings* sections of the products' labeling and Medication Guide. *www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm*

FOOTNOTES:

[1] Early Communication about an Ongoing Safety Review.

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