Health Canada Santé Canada

Canadian Adverse Drug Reaction Newsletter

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Therapeutic Products Programme

IN THIS ISSUE:

Bupropion (Zyban®, sustained-release tablets): reported adverse reactions

Bupropion (Zyban®, sustained-release tablets) has been available in Canada since August 1998. Its use is recommended, in combination with the introduction of behavioural changes, to help people quit smoking.[1]

Sustained-release bupropion is also sold under the name Wellbutrin SR® for the relief of symptoms of depression. However, this paper will not cover adverse reactions associated with Wellbutrin SR®.

Between Aug. 18 and Dec. 1, 1998, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 48 reports of suspected adverse reactions to bupropion taken to quit smoking (patients included 15 men, 31 women and 2 people sex unknown; average age 36 [range 27 to 81] years).

In the 48 reports, 144 adverse reactions were noted, the most frequent of which were pruritus (9), urticaria (7), edema (7), tremors (6), dizziness (5), insomnia (5) and anxiety (5) (Table 1). Sixteen of the reports described serious events, resulting in patients being admitted to hospital or having their hospital stay extended (n = 8), death (n = 1), convulsions (n = 3) or a major medical intervention (n = 4).

There is a risk of convulsions associated with taking bupropion to quit smoking.[1] The CADRMP received 3 reports of convulsions in patients taking Zyban®. One of the patients had a history of alcohol dependence and was taking 600 mg of Zyban® daily for 15 days before experiencing convulsions. In general, convulsions are associated with the Zyban® dose, the use of the drug in conjunction with other drugs and/or the patient's medical history or clinical features.[1] Therefore, the maximum recommended dose of bupropion is 300 mg/d, divided in 2 doses administered at least 8 hours apart.[1]

Adverse cardiovascular reactions were also reported. Patients taking Zyban® experienced palpitations (2), tachycardia (2), angina (1) and myocardial infarction (1). In the last case, a 52-year-old man died following myocardial infarction. He had a history of alcohol dependence and serious coronary artery disease. He had taken 300 mg/d (higher initial dose than that recommended by the manu-

Table 1: Suspected adverse reactions to bupropion (Zyban®) reported to the CADRMP between Aug. 18 and Dec. 1, 1998

System	Description of adverse reactions*
Central and peripheral nervous system	Tremor (6), dizziness (5), hypoesthesia (3), stupor (3), paralysis (2), convulsions grand mal (2), coordination abnormal (2), hyperkinesia (2), dyskinesia (1), dysesthesia (1), vertigo (1), speech disorder (1), headache (1), convulsions (1), paresthesia (1)
Dermatological	Pruritus (9), urticaria (7), rash (4), rash erythematous (4), erythema multiforme (2), Stevens–Johnson syndrome (1), rash maculopapular (1), skin discoloration (1)
Body	Edema (7), chest pain (3), face edema (2), allergic reaction (2), malaise (2), fatigue (2), fever (1), condition aggravated (Bell's palsy) (1), asthenia (1), sensation of warmth (1), cold extremities† (1), edema peripheral (1), mouth edema (1), pharynx edema (1)
Psychiatric	Insomnia (5), anxiety (5), suicidal ideation† (3), hallucination (3), aggressive reaction (1), anorexia (1), paranoia (1), confusion (1), depression (1), nervousness (1), concentration impaired (1), agitation (1)
Cardiovascular	Palpitations (2), tachycardia (2), flushing (1), myocardial infarction (1), angina pectoris (1)
Gastrointestinal	Nausea (4), vomiting (3), dysphagia (3), dyspepsia (1)
Respiratory	Dyspnea (3), hyperventilation (1), rhinitis (1)
Musculoskeletal	Arthralgia (1), arthropathy (1), myalgia (1)
Ophthalmic	Vision abnormal (3), mydriasis (1), photophobia (1)
Other	Ear ache (1), epistaxis (1)

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program, ADR = adverse drug reaction.
*Based on the "preferred term" in the World Health Organization (WHO) *Adverse Reaction Dictionary*.
†Terminology other than WHO terminology was used.

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facturer) for 2 days before he died. The patient was not taking other drugs.

Certain adverse cardiovascular reactions were noted with immediate-release bupropion, a formulation not available in Canada. From the reports received, the risk of such reactions with the sustained-release formulation cannot be completely ruled out.

Finally, extreme caution must be observed before administering Zyban® in conjunction with certain other drugs.[1] Two suspected cases of adverse reactions to a bupropion–paroxetine combination were reported. Nausea, vomiting, visual hallucinations and dizziness were reported 2 days after bupropion therapy was started in a 48-year-old woman who had also been taking paroxetine and estrogen replacement therapy for about a year. In the other case, a 27-year-old man experienced tachycardia, anxiety, tremors, mydriasis, blurred vision and photophobia while taking combination therapy with bupropion and paroxetine (duration of therapy unknown). He was also taking clobazam and trazodone. In both cases, symptoms disappeared after bupropion therapy was stopped.

Bupropion is a new pharmacological alternative for patients who want to quit smoking. It can be used alone or in combination with transdermal nicotine patches; the recommended duration of therapy is 7 to 12 weeks.[1] Bupropion is, however, associated with certain adverse reactions and precautions, which must be observed before administering it. According to the product monograph, the most frequent adverse reactions — insomnia and dry mouth — occur in 31% and 11% of patients respectively.[1] The adverse reactions that most often lead to a cessation of bupropion therapy include central nervous system disturbances (especially tremors) and dermatological reactions.[1]

The combined use of Zyban® and Wellbutrin SR® or any other drug containing bupropion is contraindicated, since the occurrence of convulsions is related to the bupropion dose. Health professionals should consult the product monograph for more information.

Written by: Sylvie Hébert, BPharm, Québec Regional ADR Centre.

Reference

1. *Zyban®, bupropion hydrochloride; sustained-release tablets* [product monograph]. Mississauga (ON): Glaxo Wellcome Inc.; 1998.

Adverse drug reaction reporting – 1998

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 4663 reports of adverse drug reactions (ADRs) in 1998. The ADRs were reported for the most part by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to the CADRMP or indirectly through one of the other sources (Table 1).

The increase in the number of reports received through regional ADR centres may be related to increased awareness of physicians and pharmacists of these centres and the opening of the Ontario Regional ADR Centre in September 1998. A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2.

Of the ADRs reported, 2079 reports were classified as serious. A serious ADR is defined in the Food and Drugs Act and Regulations as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."

The CADRMP would like to thank all who have reported ADRs for their contribution to the program.

Written by: Heather Sutcliffe, BScPharm, Bureau of Drug Surveillance.

Immune globulin intravenous products — notice to hospitals

A safety warning was issued by the Bureau of Drug Surveillance on Nov. 27, 1998, regarding precautions that should be taken to reduce the risk of acute renal failure (ARF) associated with the administration of human immune globulin intravenous (IGIV) products.

The US Food and Drug Administration received over 114 reports of cases of renal dysfunction or ARF, 17 of which resulted in death that may or may not have been caused by administration of IGIV products.[1] The majority of the ARF-associated adverse events reported in the US

tTable 1: Source of reports of adverse drug reactions (ADRs) received by the CADRMP in 1997 and 1998

	No. (and %) of reports received			
Source	1997		1998	
Manufacturer	1549	(38.7)	2200	(47.2)
Regional centre	993	(24.8)	1464	(31.4)
Hospital	671	(16.7)	501	(10.7)
Pharmacist	404	(10.1)	291	(6.2)
Physician	151	(3.8)	122	(2.6)
Other*	238	(5.9)	85	(1.8)
Total	4006	(100.0)	4663	(100.0)

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program.
*Includes, but not limited to, professional associations, nursing homes, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of ADR reports by type of reporter (originator)

Reporter	No. (and %) of reports	
Pharmacist	1751	(37.6)
Physician	1265	(27.1)
Health professional*	757	(16.2)
Consumer/patient	331	(7.1)
Nurse	291	(6.2)
Other	268	(5.7)
Total	4663	(100.0)

*Type not specified in report.

were associated with IGIV products containing sucrose.[1] In the last 10 years, Health Canada has not released any lots of IGIV products containing sucrose. As of this report, no ADRs associated with renal dysfunction or ARF have been reported in Canada.

The full report on this safety warning can be found on Health Canada's Web site (**www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/notices/igiv-not.html**).

Written by: Vicky Hogan, MSc, Bureau of Drug Surveillance.

Reference

1. *Dear Doctor letter: Important drug warning*. Washington: US Food and Drug Administration, Center for Biologics Evaluation and Research. Available: www.fda.gov/medwatch/safety/1998/igiv.htm [accessed 1999 Feb 19]

Tolcapone (Tasmar™)

On Nov. 20, 1998, Health Canada suspended the sale of tolcapone (Tasmar™), the first approved reversible catechol-O-methyl transferase inhibitor indicated as an adjunct to levodopa-decarboxylase inhibitors in the treatment of Parkinson's disease. This action was based on emerging safety concerns regarding hepatotoxicity and potentially fatal fulminant hepatitis associated with tolcapone therapy. This regulatory decision was communicated to health care professionals in "Dear Healthcare Professional" and "Dear Pharmacist" letters issued on Nov. 23, 1998, by the manufacturer, Hoffman–La Roche. Also, Health Canada posted an advisory about tolcapone on its Web site (**www.hc-sc.gc.ca/english/archives/warnings/98_88e.htm**).

Continued availability of tolcapone through the Special Access Programme (SAP) was organized on a limited and exceptional basis for 1) the safe discontinuation of tolcapone therapy and 2) extraordinary cases involving patients already receiving tolcapone therapy for whom, in the opinion of their physician, the benefits of continued treatment outweighed the risks. The procedure and criteria for physicians to obtain access to tolcapone through SAP, in addition to safety considerations regarding the continuation of tolcapone therapy, were outlined in "Dear Healthcare Professional" and "Dear Pharmacist" letters issued by Health Canada on Dec. 4, 1998. As of January 1999, SAP has received about 200 requests for tolcapone.

Written by: Susan Robertson, MD, Bureau of Drug Surveillance.

COMMUNIQUÉ

The purpose of this section is to increase awareness of ADRs recently reported to the CADRMP. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting. (The terminology used for expressing reactions is based on the World Health Organization's *Adverse Reaction Dictionary* using the "preferred term.")

Olanzapine (Zyprexa®): priapism

Priapism necessitating admission to hospital was reported during olanzapine therapy.

If you have observed comparable cases or any other serious events, *please report them* to the Adverse Drug Reaction Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 0201C2, Ottawa ON K1A 1B9; fax 613 957-0335; or to a participating regional ADR centre.

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. For these reasons, most adverse drug reactions (ADRs) can be considered only to be suspicions, for which a proven causal association has not been established. Because there is gross underreporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless invaluable as a source of potential new and undocumented signals. For this reason, Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles.

Newsletter Editors: Ann Sztuke-Fournier, BPharm, and Lynn Macdonald, BSP, Bureau of Drug Surveillance.

We thank the Chair of the Expert Advisory Committee on Pharmacovigilance, and the staff of the Adverse Drug Reaction Regional Centres and the Therapeutic Products Programme for their valuable comments.

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Health Canada Santé Canada

Canadian Adverse Drug Reaction Monitoring Program

Report of suspected adverse reaction due to drug products marketed in Canada (Vaccines excluded)

Therapeutic Products Programme

PROTECTED

• **La version française de ce document est disponible sur demande.**

A. Patient Information

1. Patient identifier	2. Age at time of reaction	3. Sex	4. Height	5. Weight
	_____ or	☐ Male	_____ feet	_____ lbs
Chart Number	**Date of birth** DD MM YYYY	☐ Female	or _____ cm	or _____ kgs

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)

- ☐ Death _____ (dd / mm / yyyy)
- ☐ Disability
- ☐ Life-threatening
- ☐ Congenital malformation
- ☐ Hospitalization
- ☐ Required intervention to prevent damage / permanent impairment
- ☐ Hospitalization - prolonged
- ☐ Other: _____

2. Date and time of reaction DD MM YYYY

3. Date of this report DD MM YYYY

4. Describe reaction or problem

5. Relevant tests / laboratory data (including dates (dd / mm / yyyy)

6. Other relevant history, including preexisting medical conditions (e.g. allergies, pregnancy, smoking and alcohol use, hepatic / renal dysfunction)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.

C. Suspected drug product(s) (See "How to report" section on reverse)

1. Name (give labelled strength & manufacturer, if known).

#1 _____

#2 _____

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1	#1 From (dd / mm / yyyy) - To (dd / mm / yyyy)
#2	#2

4. Indication for use of suspected drug product	5. Reaction abated after use stopped or dose reduced
#1	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Reaction reappeared after reintroduction
#1 _____	#1 (dd / mm / yyyy) _____	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

9. Concomitant drugs (name, dose, frequency and route used) and therapy dates (dd / mm / yyyy) (exclude treatment of reaction)

10. Treatment of adverse reaction (drugs and / or therapy), **including dates** (dd / mm / yyyy)

D. Reporter (See "Confidentiality" section on reverse)

1. Name, address & phone number.

2. Health professional?	3. Occupation	4. Also reported to manufacturer?
☐ Yes ☐ No		☐ Yes ☐ No

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