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Canadian Adverse Reaction Newsletter

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www.healthcanada.gc.ca/carn

In this issue

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to stimulate adverse reaction reporting as well as to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

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Atypical antipsychotics and agranulocytosis

Atypical antipsychotic medications are indicated for the management of symptoms of schizophrenia and other related psychotic disorders. Clozapine was the first atypical antipsychotic drug and was marketed in Canada in 1991. Since then, 4 others have been marketed: olanzapine, quetiapine, risperidone and ziprasidone.[1–5]

Granulocytopenia and agranulocytosis have been shown to occur in association with clozapine; therefore, use of this drug requires regular white blood cell and differential counts.[1] No cases of drug-induced agranulocytosis were reported during the premarketing clinical trials for olanzapine, quetiapine, risperidone and ziprasidone.[2–5] However, recent evidence suggests that these drugs may also be associated with an occurrence of agranulocytosis, but not to the extent of clozapine.[6–9]

Agranulocytosis is a life-threatening condition owing to an increased vulnerability to infection and requires immediate medical attention.[10] According to the Council for International Organizations of Medical Sciences (CIOMS),[10] the term granulocytopenia is used when granulocyte counts are less than 1.5×10^9/L and no distinctions can be made between eosinophilic and basophilic cells from neutrophilic granulocytes. Neutropenia is defined as an absolute neutrophil count of less than 1.5×10^9/L, and severe neutropenia as a count of less than 0.5×10^9/L. Agranulocytosis is defined as a disorder in which severe neutropenia is associated with the sudden onset of signs and symptoms of bacterial infection, such as sore throat, fever, malaise, prostration and typical presentation with oropharyngeal or anorectal lesions.

Agranulocytosis is an idiosyncratic adverse reaction (AR) resulting from the failure of production of neutrophils in the bone marrow, from their peripheral destruction, or both. Even though the pathogenesis of drug-induced agranulocytosis is not completely understood, studies have suggested that it is mediated by immunoallergic or toxic mechanisms.[8]

As of Nov. 30, 2008, Health Canada received 69 reports of granulocytopenia, neutropenia and agranulocytosis suspected of being associated with the use of olanzapine, quetiapine and risperidone (Table 1). No reports were identified about ziprasidone, which was marketed in January 2008. According to the CIOMS definitions, there were 14 cases of agranulocytosis, 6 cases of severe neutropenia, 45 cases of neutropenia and 4 cases of granulocytopenia. Concomitant medical conditions (e.g., cancer, lupus, Tourette syndrome, depression and cardiovascular disease) or concomitant use of other medications (e.g., typical and atypical antipsychotics, antidepressants, anticonvulsants, anti-inflammatory and antineoplastic drugs), or both, was reported in many of these cases.

Health care professionals should be

Table 1: Summary of the 69 reports of granulocytopenia, neutropenia and agranulocytosis suspected of being associated with atypical antipsychotics received by Health Canada since date of marketing to Nov. 30, 2008*

Variable	Olanzapine	Risperidone	Quetiapine	Ziprasidone
Date marketed (notified) in Canada	November 1996	September 1999	January 2001	January 2008
Approved indications	• Schizophrenia and related disorders • Bipolar disorders	• Schizophrenia • Severe dementia • Bipolar disorders	• Schizophrenia • Bipolar disorders	• Schizophrenia and related disorders • Bipolar disorders
Adverse reaction reports†‡	Granulocytopenia: 2 Neutropenia: 14 Agranulocytosis: 4 Total: 20	Granulocytopenia: 2 Neutropenia: 15 Severe neutropenia: 1 Agranulocytosis: 6 Total: 24	Neutropenia: 16 Severe neutropenia: 5 Agranulocytosis: 4 Total: 25	No reports
No. of female/male patients	8/12	9/14§	15/8¶	NA
Age of patients, yr	15–79	9–85	14–81	NA

Note: NA = not applicable.
*These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the health product was on the market has been taken into consideration.
†Reaction terms are listed according to the *World Health Organization Adverse Reaction Terminology* (WHOART) or the *Medical Dictionary for Regulatory Activities* (MedDRA).
‡Only the most severe AR of the 4 types of blood dyscrasia is accounted per report.
§Sex not reported in 1 case.
¶Sex not reported in 2 cases.

aware of the risk of agranulocytosis suspected of being associated with atypical antipsychotics. Increased awareness leading to early detection and treatment is key to managing this life-threatening AR. Patients should be informed about the importance of symptoms such as fever, sore throat or other infections, and be advised to see their doctor immediately if these symptoms occur.[8] Health care professionals are encouraged to report any ARs suspected of being associated with the use of atypical antipsychotics to Health Canada at www.healthcanada.gc.ca/medeffect.

Marc Poitras, MSc, PhD, MBA, Health Canada

References

1. *Clozaril (clozapine)* [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2007.
2. *Zyprexa (olanzapine)* [product monograph]. Toronto (ON): Eli Lilly Canada Inc.; 2008.
3. *Seroquel (quetiapine fumarate)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2008.
4. *Risperdal (risperidone)* [product monograph]. Toronto (ON): Janssen-Ortho Inc.; 2008.
5. *Zeldox (ziprasidone)* [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2008.
6. Flanagan RJ, Dunk L. Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol* 2008; 23 Suppl 1:27-41.
7. Andrès E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. *Curr Opin Hematol* 2008;15(1):15-21.
8. Garbe E. Non-chemotherapy drug-induced agranulocytosis. *Expert Opin Drug Saf* 2007;6(3):323-35.
9. Duggal HS, Singh I. Psychotropic drug-induced neutropenia. *Drugs Today (Barc)* 2005;41(8): 517-26.
10. Council for International Organizations of Medical Sciences. *Reporting adverse drug reactions: definitions of terms and criteria for their use*. Geneva: The Council; 1999.

Adverse reaction and incident reporting — 2008

Canada Vigilance Program

The Canada Vigilance Program collects reports of suspected adverse reactions (ARs) to health products (pharmaceuticals, biologics, natural health products, radiopharmaceuticals and biotechnology products). This new AR monitoring program and database was implemented within Health Canada in March 2008 and allows for more sophisticated breakdown of data and reports. Further information about the program and its database can be found at www.hc-sc.gc.ca/dhp-mps/medeff/vigilance-eng.php.

In 2008, Health Canada received 20 360 domestic AR reports (Table 1), of which 69.2% were considered to be serious.* Domestic AR cases received by product type are provided in Table 2.

In Canada, Market Authorization Holders (MAHs) are required to submit AR reports received in accordance with the requirements of the *Food and Drugs Act* and Regulations. MAHs are

*In the *Food and Drugs Act* and Regulations, a serious AR is defined as "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death." A serious unexpected AR is defined as "a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug."

required to send, within 15 days, all reports of serious ARs that have occurred in Canada (domestic) and all reports of serious unexpected ARs that have occurred outside Canada (foreign) to the Canada Vigilance Program. In 2008, MAHs submitted 71.8% of all the domestic reports received. The remaining reports were received directly from the community and hospitals (Table 1).

The number of domestic AR reports was 15.6% higher in 2008 than in 2007 (Fig. 1). The majority of domestic cases reported to both MAHs and Health Canada originated from health care professionals (Table 3).

The number of foreign AR reports received from MAHs was 241 417 (Fig. 2). At this time, foreign reports are not included in the Canada Vigilance database.

Health Canada would like to thank all who have contributed to the Canada Vigilance Program and encourages the continued support of postmarketing surveillance through AR reporting. Any suspected ARs associated with the use of health products can be reported to the Canada Vigilance Program by one of the following methods:

- Call toll free at 1-866-234-2345
- Report online at www.healthcanada.gc.ca/medeffect
- Complete a Canada Vigilance Reporting Form and:
  - fax it toll free (1-866-678-6789) or
  - mail it to:
    Canada Vigilance Program
    Health Canada
    Address Locator 0701C
    Ottawa ON K1A 0K9

Postage-paid labels, the Canada Vigilance Reporting Form and the AR reporting guidelines ("Guidelines — Voluntary Reporting of Suspected Adverse Reactions to Health Products by Health Professionals and Consumers") are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect. The reporting form is also located in the back of the *Compendium of Pharmaceuticals and Specialties* (CPS).

Table 1: Number of domestic reports of adverse reactions by source in 2008

Source	No. (%) of reports
MAH	14 611 (71.8)
Community*	4 604 (22.6)
Hospital	1 013 (5.0)
Other	132 (0.6)
Total	20 360 (100.0)

Note: MAH = Market Authorization Holder.
*Consumer, patient and non-hospital-based health care professionals.

Table 2: Number of domestic cases* of adverse reactions by product type in 2008

Product type	No. (%) of cases
Pharmaceuticals	11 596 (71.3)
Biotechnology products	3 303 (20.3)
Biologics	792 (4.9)
Radiopharmaceuticals	292 (1.8)
Natural health products	289 (1.8)
Total†	16 272 (100.0)

*Cases result from the merge of initial and duplicate reports.
†Total number of cases includes one suspect product identified in each adverse reaction case. A case may include more than one suspect product.

Table 3: Number of domestic cases* of adverse reactions by type of originating reporter in 2008

Reporter type	No. (%) of cases
Physician	4 091 (25.1)
Consumer	3 132 (19.2)
Pharmacist	2 893 (17.8)
Health professional†	2 421 (14.9)
Patient	1 719 (10.6)
Nurse	1 489 (9.2)
Coroner/medical examiner	251 (1.5)
Lawyer	23 (0.1)
Dentist	4 (0.02)
Naturopath	3 (0.02)
Other	246 (1.5)
Total‡	16 272 (100.0)

*Cases result from the merge of initial and duplicate reports.
†Type not specified in report.
‡Total number of cases may include more than one suspect product per adverse reaction case.

Medical device incidents

Medical device incidents are collected by the Health Product and Food Branch Inspectorate and are entered into the medical device system. The Inspectorate is responsible for compliance monitoring activities for a broad spectrum of regulated health products, including medical devices that range from adhesive bandages to pacemakers. It is also responsible for the delivery of a national compliance and enforcement program in an effort to minimize health risks to Canadians while maximizing the safety of health products. A major component of this program involves the collection, review and follow-up of incidents related to medical devices, which are reported to the Inspectorate via the submission of mandatory and voluntary problem reports. Manufacturers and importers are required to submit mandatory reports as per section 59–61 in the Medical Device Regulations (www.laws.justice.gc.ca/en/showdoc/cr/SOR-98-282/20090205); voluntary reports are submitted mostly

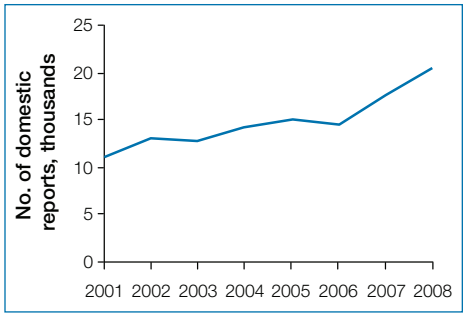

Fig. 1: Number of domestic reports of adverse reactions received by Health Canada from 2001 to 2008.

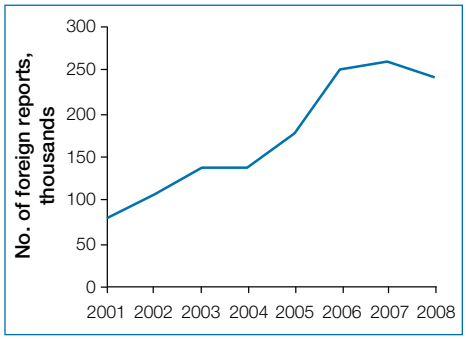

Fig. 2: Number of foreign reports of adverse reactions received by Health Canada from 2001 to 2008.

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined.
Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

by health care professionals and patients/users. In 2008, a total of 4491 incidents were entered into the medical device system. Of these reports, 4091 (91.0%) were mandatory and 400 (9.0%) voluntary.

- Information on mandatory and voluntary reporting of medical device incidents can be found at: www.hc-sc.gc.ca/dhp-mps/compli-conform/prob-report-rapport/rep_md_prob-rap_inc_im_tc-tm-eng.php/.
- Completed Medical Devices Problem Report forms can be submitted by email as attachments to: mdpr@hc-sc.gc.ca.
- Please include the acronym "MDPR" in the subject line of the email in order to generate an automated confirmation of receipt by the Inspectorate.

Jennifer Lo, BSc, BA; Fannie St-Gelais, PhD; Shawn Hopewell, MSc, Health Canada

Cough and cold products

In December 2008, Health Canada issued a public advisory concerning the use of certain cough and cold medicines for children under the age of 12.

- Health Canada advises the public that certain over-the-counter cough and cold medicines should not be used in children under 6 years of age.
- In addition, cough and cold medicines marketed for use in children will require enhanced labelling and packaging.

Health Canada's new recommendations follow a review of additional data, including the input of a Scientific Advisory Panel convened in March 2008. Health Canada is working with manufacturers to revise the labelling of cough and cold products.

The public advisory, including the list of affected active ingredients, is available at www.healthcanada.gc.ca/coughandcold.

Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

5-Hour Energy drink: suspected association with a cardiovascular adverse reaction

Energy drinks are popular and are widely available on the Canadian market. They are classified as natural health products and are promoted to provide energy and contribute to mental alertness and physical performance. 5-Hour Energy drink is not authorized for sale in Canada. However, it is available in a 2-ounce (59-mL) bottle and contains among its ingredients niacinamide 30 mg, vitamin B_6 40 mg, folic acid 400 µg, vitamin B_{12} 500 µg, sodium 10 mg, and "Energy Blend" (citicoline, glucuronolactone, *N*-acetyl L-tyrosine, L-phenylalanine, taurine, malic acid, caffeine). Labelling on the bottle states "For maximum energy, drink entire bottle at one time. For moderate energy, drink a half bottle or less" and "Caution: contains about as much caffeine as a cup of coffee." However, caffeine amounts in coffee vary according to brewing methods and coffee type. A plain brewed 250-mL cup of coffee contains 95 mg of caffeine.[1]

Health Canada received a report of a 55-year-old man who drank a 5-Hour Energy drink for lethargy. About 30 minutes to an hour later, he felt his heart beating rapidly and had chest pain. At the emergency department, his systolic blood pressure was 200 mm Hg. The patient was known to have a heart condition and was taking rosuvastatin, hydrochlorothiazide, acetylsalicylic acid, quinapril and long-acting diltiazem. He was released from hospital the same day after treatment with lorazepam.

Health Canada encourages the reporting of similar suspected adverse reactions to the Canada Vigilance Program (www.healthcanada.gc.ca/medeffect).

Reference

1. *How much caffeine is in your daily habit?* Mayo Foundation for Medical Education and Research; 2007. Available: www.mayoclinic.com/health/caffeine/AN01211 (accessed 2008 Dec. 23).

Health Canada / Santé Canada

Canada Vigilance

Report of suspected adverse reaction due to **health products*** marketed in Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

The form should be printed and faxed toll free to:
1 866 678-6789 or mailed as per instructions provided.

PROTECTED B**
(when completed)

La version française de ce document est disponible à: http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-fra.php

A. Patient Information (See " Confidentiality" section)

1. Identifier	3. Sex	4. Height	5. Weight
2. Age at time of reaction	☐ Male ☐ Female	_____ feet or _____ cm	_____ lbs or _____ kgs

B. Adverse Reaction

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

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

2. Date of reaction			3. Date of this report		
YYYY	MM	DD	YYYY	MM	DD

4. Describe reaction or problem

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

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

C. Suspected Health Product(s) (See "How to report" section)

1. Name (give labeled strength & manufacturer, if known)
1
2

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

4. Indication for use of suspected health 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 (yyyy/mm/dd)	# 1 ☐ Yes ☐ No ☐ Doesn't apply
# 2	# 2	# 2 ☐ Yes ☐ No ☐ Doesn't apply

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

10. Treatment of adverse reaction (medications and / or other therapy), **include dates** (yyyy/mm/dd)

D. Reporter Information (See " Confidentiality" section)

1. Name, address & phone number

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

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.
*** Use this form to report suspected adverse reactions to pharmaceuticals, biologics (including fractionated blood products, as well as therapeutic and diagnostic vaccines), natural health products or radiopharmaceuticals.**
**** As per the Treasury Board of Canada Secretariat Government Security Policy.**

HC/SC 4016 (10/08)

Canada

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined.
Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Canadian Adverse Reaction Newsletter: distribution changes

The January 2009 issue of the *Canadian Adverse Reaction Newsletter* (*CARN*) was the last issue to be published in the *Canadian Medical Association Journal* (*CMAJ*). *CARN* continues to be available on the MedEffect™ Canada website and by subscribing to MedEffect™ e-Notice. Print versions are available to interested individuals upon request. In addition, in January 2009, highlights of *CARN* were faxed to hospitals and medical clinics. Highlights of *CARN* can also be found in various health professional journals.

- To receive *CARN* free by email, subscribe to Health Canada's **MedEffect™ e-Notice** at: **www.healthcanada.gc.ca/medeffect**.
- To receive print versions of future issues of *CARN*, contact the *CARN* Editorial Team by mail (see address at right), fax (613-952-7738) or by email (mhpd_dpsc@hc-sc.gc.ca).
- Electronic versions of the latest issue and previously published issues of *CARN* are available at: **www.healthcanada.gc.ca/carn**.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Nov. 13, 2008 – Mar. 10, 2009)

Date	Product	Subject
Mar 5	Oral sodium phosphate products	Warning — purgative dose may lead to kidney injury
Mar 5 & 2	Topical anesthetics	Information — serious adverse events
Mar 5	Foreign products	Foreign product alerts
Feb 25	Foreign products	Foreign product alerts
Feb 23	Desferrioxamine Mesilate BP	Recall of two lots of 500-mg and 2-g formats
Feb 20	Raptiva	Suspension of marketing
Feb 17	PregVit folic 5 & PregVit	Check product packaging
Feb 16	Toothbrushes	Counterfeit toothbrushes
Feb 13	Tysabri	Information — Progressive Multifocal Leukoencephalopathy (PML)
Jan 30	Foreign products	Foreign product alerts
Jan 13 & Dec 22	Botox / Botox Cosmetic	Additional safety information
Jan 7 & 2	Fentanyl transdermal systems	Changes to the dose-conversion guidelines
Jan 6	Champix	Important safety information
Dec 31	Dobutamine Hydrochloride	Recall of certain lots
Dec 23	Piperacillin / Tazobactam	Recall of lot 7101490
Dec 22	Raptiva	Association with serious infections in patients with psoriasis
Dec 19	Actos	Updated labelling for diabetes drug and risk of heart failure
Dec 18	Cough and cold products	Health Canada's decision on cough and cold products
Dec 17 & 12	Tarceva	Important safety information
Dec 16	Avastin	Reports of ophthalmologic adverse reactions following off-label intravitreal use
Dec 16 & 15	Blood glucose meters	Risk of inaccurate blood glucose readings with certain glucose meters
Nov 27	Kwan Loong Medicated Oil	Unauthorized natural health product may cause adverse health effects
Nov 26	Firm Dose and Granite Rooster	Warning not to use these unauthorized products
Nov 18	MabCampath	Infection-related deaths
Nov 17	Foreign products	Foreign product alerts
Nov 11	Liko Uno Patient Lift	Urgent medical device correction

Advisories are available at www.healthcanada.gc.ca/medeffect.

Canadian Adverse Reaction Newsletter

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Suggestions?

Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

Reporting Adverse Reactions

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