THE MANITOBA PHARMACEUTICAL ASSOCIATION
200 TACHE AVENUE, WINNIPEG, MANITOBA R2H 1A7 PH: 233-1411 FAX: 237-3468

ANNUAL GOLF TOURNAMENT

Kingswood Golf & Country Club

LaSalle, Manitoba (6 minutes from South Perimeter, South on Hwy. 330)

TUESDAY, SEPTEMBER 11, 2012

The Tournament is restricted to the following. Please check one:

Pharmacist	_____
MPhA/M.S.P. Staff	_____
Pharmaceutical Rep	_____
Wholesalers	_____
Spouses of Above	_____
Pharmacy Staff	_____
MPhA Special Guests	_____

Prizes for best gross and net scores will be up for grabs, as well as many great prizes for not having the best gross and net scores. **SHOTGUN START AT 12:00 Noon** with dinner at 5:30 p.m. THE PUTTING CONTEST will be held to raise funds for the "Canadian Foundation for Pharmacy".

Hole sponsorship is *$300.00 per hole* which includes a sign displayed on the course indicating your support.

~ LOTS OF PRIZES ~

Hole Sponsorship & Prizes: If you wish to **provide a donation or sponsor a hole** for the event, please forward to the M.Ph.A. Office, 200 Tache Avenue, or call the office and we can arrange to have them picked up. Phone 233-1411 ask for Pamela or email pgordon@mpha.mb.ca. **All sponsors will be provided with as much exposure and recognition at the event as possible.**

M.Ph.A. GOLF TOURNAMENT REGISTRATION FORM

NAME _____

ADDRESS _____

PHONE NO. _____ **(W)** _____ **(H)** **E-mail:**_____

I will golf with: _____ **I require placement in a foursome** _____

_____

_____

Early Bird Registration Fee (Must register before August 24th): $75.00 (Includes Golf, Dinner and applicable taxes)
Registration Fee (If registering after August 24th): $85.00 (Includes Golf, Dinner and applicable taxes)
Golf Cart Reservations: to be made directly with the Kingswood Golf & Country Club at (204)736-4079.

PAYMENT MUST ACCOMPANY ALL ENTRIES - NO EXCEPTIONS
DEADLINE FOR ENTRIES IS *THURSDAY, SEPTEMBER 6, 2012*

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Your health and safety…our priority. *Votre santé et votre sécurité… notre priorité.*

Canadian Adverse Reaction Newsletter

Volume 22 • Issue 1 • January 2012

www.health.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
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Online: www.health.gc.ca/medeffect

Did you know?

To receive the **Newsletter** and health product **advisories** free by email, **subscribe** to the **MedEffect™ e-Notice** at **www.health.gc.ca/medeffect**

Second-generation antipsychotics and cardiometabolic adverse reactions in children and adolescents

Key points

- Health Canada received 29 reports of cardiometabolic adverse reactions suspected of being associated with second-generation antipsychotics (SGAs) in children and adolescents under 18 years old.
- In Canada, no SGAs are authorized for use in children or adolescents, with one recent exception authorized for use only in adolescents 15 to 17 years old for the treatment of schizophrenia.
- The cardiometabolic effects of SGAs, which include age-inappropriate weight gain, hypertension, and lipid and glucose abnormalities, have been found to vary by SGA agent.

Excess weight and obesity in the general population are increasing problems throughout the Western world, and this rise has also been observed in children and adolescents.[1] Weight gain and obesity are known to be associated with diabetes, dyslipidemia and hypertension.[2] In addition, weight gain is a well-established adverse reaction (AR) to second-generation antipsychotics (SGAs).[1]

In Canada, there are 7 marketed second-generation antipsychotics: clozapine, risperidone, olanzapine, quetiapine, paliperidone, ziprasidone and aripiprazole. Their date of marketing ranges from 1991 (clozapine) to 2009 (aripiprazole).

Recently, aripiprazole (Abilify) was authorized for the treatment of schizophrenia in adolescents 15 to 17 years old.[3] Previously, there were no authorized indications for the use of SGAs in children or adolescents under 18 years of age in Canada. Pediatric drug use, in many circumstances, has been based primarily on information extrapolated from studies involving adults, as well as from other types of scientific evidence, including case reports, open studies of clinical experience and controlled clinical trials.[4,5] Second-generation antipsychotics have been prescribed for children and adolescents with mental health problems such as schizophrenia, bipolar I disorder, autism, pervasive developmental disorder, disruptive behaviour disorders (including conduct disorder and attention-deficit hyperactivity disorder), developmental disabilities and Tourette syndrome.[6] The use of these drugs in the pediatric population has increased substantially over the last decade.[6–8] According to one estimate, antipsychotic drug prescriptions for children and youth in

Table 1: Summary of 29 reports of cardiometabolic adverse reactions (ARs) suspected of being associated with second-generation antipsychotics in children and adolescents under 18 years of age submitted to Health Canada as of June 30, 2011*

Drug (year of marketing in Canada)	AR; no. of times reported				
	Weight gain	Hyperglycemia or new-onset diabetes	Hypertension	Hyperlipidemia	Total†
Clozapine (1991)	1	0	2	0	3
Risperidone (1993)	5	5	2	2	14
Olanzapine (1996)	9	5	2	1	17
Quetiapine (1997)	2	2	1	0	5

***These data cannot be used to determine the incidence of ARs because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Some reports may contain one or more reactions and one or more suspected products. Therefore, the total number of ARs does not reflect the total number of case reports.

Canada increased by 114% from 2005 to 2009.[4] Despite this increased use, data regarding their safety are limited.[2]

The cardiometabolic effects of SGAs in pediatric patients, including age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities, are of concern.[8] Furthermore, children and adolescents with mental health problems often have multiple cardiovascular risk factors, including poor nutrition, inadequate exercise, substance abuse and lack of adequate health care monitoring.[2,9] Some studies have shown that youth using antipsychotic agents may be at a higher risk of weight gain and metabolic effects than adults who use the same drugs.[2,7,10] If weight gain is established in youth, it tends to persist into adulthood.[10]

Because of differences in absorption, distribution and metabolism of antipsychotics in the pediatric population, higher doses per weight are required than in adults to achieve similar efficacy.[2] Cardiometabolic effects are problematic during childhood because they tend to be predictors of adult obesity, metabolic syndrome, hypertension, cardiovascular morbidity and malignant disease.[2,7,8]

Adverse effects such as weight gain have been found to vary significantly by SGA agent. Clozapine and olanzapine seem to be associated with the highest risk of clinically significant weight gain in children and adults.[1,2,7] Risperidone and quetiapine generally show modest risk, whereas ziprasidone and aripiprazole are associated with the lowest risk. Limited data are available for paliperidone.[4] The risk of lipid elevation and increased blood sugar appears to be greatest with olanzapine.[11]

As of June 30, 2011, Health Canada received 29 reports of cardiometabolic ARs in children and adolescents under 18 years suspected of being associated with clozapine (n = 3), risperidone (n = 13), olanzapine (n = 10) and quetiapine (n = 4) (Table 1).* None of the reports implicated paliperidone, ziprasidone or aripiprazole. The case reports included one or more of weight gain, hyperglycemia or new-onset diabetes, hypertension and hyperlipidemia. Of these cases, 21 involved boys and 7 involved girls (sex not specified in one report). The median age of the patients was 14 years. Some reports indicated the use of concomitant medications known to cause weight gain.

There appears to be an increase in off-label use of SGAs in children and adolescents for the management of a number of mental health disorders. The issue of cardiometabolic ARs in children and adolescents taking SGAs has been identified in the literature.[2,4,6,7,11] In addition, the cardiometabolic effects of SGAs have been found to vary by SGA agent. Health Canada encourages the reporting of ARs suspected of being associated with the use of SGAs through the Canada Vigilance Program at www.health.gc.ca/medeffect.

*One of the 29 reports identified 2 SGAs as suspect drugs.

David Pfeiffer, MD, CCFP; Danielle Brûlé-Brown, MD, CCFP, FCFP, Health Canada

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Prescription drugs and pediatric patients

Key points

- The use of drugs to treat pediatric health conditions is increasing.
- The safety and efficacy of medications may be significantly different in pediatric patients than in adult patients.
- Health Canada recognizes the need to strengthen information related to pediatric health.

In the past, treatment decisions involving the use of drugs in infants, children and youth were often derived from the data in drug studies involving adults.[1,2] However, the safety and efficacy of medications may be significantly different in pediatric patients than in adult patients owing to differences in developmental physiology, disease pathophysiology, and developmental pharmacokinetics and pharmacodynamics.[2] This understanding has led to the use of the phrase "children are not just small adults," a statement that emphasizes the urgent need for evidence from high-quality trials involving pediatric patients.[2]

The use of drugs to treat pediatric health conditions is increasing.[3] Infants, children and youth represent nearly one-quarter of Canada's population and, on average, receive 4 prescriptions a year from a range of more than 1200 different drugs.[3,4] However, data on the efficacy and safety of most medications prescribed for pediatric patients are limited.[2,3,5]

When prescribing a medication for an "off-label" indication in infants, children or youth, health professionals may consult available sources of information, such as peer-reviewed medical literature, pediatric dosing manuals and textbooks, drug formularies at children's hospitals, community pharmacists and the relevant pharmaceutical company representatives. Nonetheless, information provided by these sources may be based more on expert opinion or local practice and experience, in the absence of experimental studies in pediatric populations.[5]

Having stated the above, drug investigations in pediatric populations can be faced with multiple challenges. Some examples include:

- defining appropriate ethical adaptations of clinical trials for studies involving infants, children and youth;[1]
- ensuring adequate sample sizes;[1,2]
- choosing objective, clinically relevant endpoints that can be measured in a valid and reliable manner;[1,2]
- overcoming technical difficulties, such as the need for frequent blood sampling;[1]
- improving pharmacoepidemiologic and pharmacovigilance practices aimed to coordinate the development of reliable information about drug benefits and harms to reduce uncertainties about the use of drugs in pediatric populations; and
- expanding the availability of age-appropriate product formulations (e.g., liquid formulations for younger patients).

Health Canada, like other regulatory authorities around the world, recognizes the need to strengthen information related to pediatric health. In pursuit of this objective, some of its key activities include:

- coordinating the development of pediatric information through the regulatory system and other means;
- coordinating how this information is made available and accessible;
- raising awareness of child health needs and safety issues related to the development and use of health products and food;
- promoting conditions that enable Canadians to make informed decisions about the health and nutrition of infants, children and youth.

To help improve safety data about health products for the pediatric population, it is important for health care providers to continue to report adverse reactions in both pediatric and adult populations to Health Canada (www.health.gc.ca/medeffect).

Marion Haas, Office of Paediatric Initiatives, Health Canada

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Canadian Paediatric Surveillance Program

Since 2004, the Canadian Paediatric Surveillance Program (CPSP), an active surveillance program of the Canadian Paediatric Society, has been collecting reports of serious and life-threatening adverse reactions (ARs), including submissions to the Canada Vigilance Program. The CPSP has been instrumental in building and maintaining a culture of reporting among its members, who number more than 2500 practising pediatricians and pediatric subspecialists. It has simplified the reporting process and increased the likelihood of AR reporting.

Adverse reaction reporting in children: update

In July 2006, the *Canadian Adverse Reaction Newsletter* (*CARN*) communicated the importance of voluntary reporting of potential adverse reactions (ARs) in children to Health Canada.[1] This article provides further details on the type of pediatric AR reports received by Health Canada in 2010. The general overview of AR reporting in 2010 for all ages appeared in the July 2011 issue of *CARN*.[2]

Through the Canada Vigilance Program, Health Canada collects reports of suspected ARs to health products (pharmaceuticals, biotechnology products, blood products and biologics, natural health products, radiopharmaceuticals, and cells, tissues and organs).

In 2010, pediatric AR reports represented 7% of a total of 22 241 cases received; the balance of reports involved adults and elderly people (72%) and people whose age was not reported (21%). Within the pediatric group, the AR distribution by subgroups was 14% for those aged less than 2 years, 44% for those 2 to 11 years and 42% for those 12 to 18 years. Boys accounted for 52% of the reports and girls for 41% (sex not stated in 7%).

The groups of suspect health products most commonly identified in AR reports for each pediatric age subgroup are listed in Tables 1, 2 and 3. Health products are classified by Anatomical Therapeutic Chemical (ATC) groups, according to the World Health Organization's ATC classification system (www.whocc.no/atc_ddd_index/). Several factors may influence the number of ARs reported for a specific health product or product type.[2] In particular, the data reflect the use of health product types within the various age subgroups.

Health Canada continues to monitor the safety profile of marketed health products and communicates, as necessary, new safety information resulting from its post-market surveillance program. Patients and health care professionals are encouraged to report ARs in infants, children and youth through the Canada Vigilance Program (www.hc-sc.gc.ca/dhp-mps/medeff/vigilance-eng.php).[1]

Marielle McMorran, BSc, BSc(Pharm), Health Canada

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Table 1: Top 10 groups of suspect health products most commonly reported in 2010 for children less than 2 years old, by Anatomical Therapeutic Chemical (ATC) group*

Health product (ATC group)	No. (%) of times reported†
Antibacterials for systemic use (J01)	16 (14.6)
Antivirals for systemic use (J05)	14 (12.7)
Immune sera and immunoglobulins (J06)	8 (7.3)
Immunosuppressants (L04)	7 (6.4)
Anti-inflammatory and antirheumatic products (M01)	6 (5.5)
Analgesics (N02)	5 (4.6)
Psychoanaleptics‡ (N06)	5 (4.6)
Antimycobacterials (J04)	4 (3.6)
Antineoplastic agents (L01)	3 (2.7)
Antiepileptics (N03)	3 (2.7)

*Solicited reports or organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) may affect the total number of ARs reported for specific products or product types.
†One case may contain one or more suspect products.
‡N06 psychoanaleptics: antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, and anti-dementia drugs.

Table 2: Top 10 groups of suspect health products most commonly reported in 2010 for children 2 to 11 years old, by Anatomical Therapeutic Chemical (ATC) group*

Health product (ATC group)	No. (%) of times reported†
Psychoanaleptics‡ (N06)	52 (17.5)
Antineoplastic agents (L01)	30 (10.1)
Antibacterials for systemic use (J01)	26 (8.8)
Corticosteroids for systemic use (H02)	21 (7.1)
Immunosuppressants (L04)	19 (6.4)
Drugs for obstructive airway diseases (R03)	18 (6.1)
Antiepileptics (N03)	15 (5.1)
Anti-inflammatory and antirheumatic products (M01)	13 (4.4)
Anesthetics (N01)	10 (3.4)
Analgesics (N02)	9 (3.0)

*Solicited reports or organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) may affect the total number of ARs reported for specific products or product types.
†One case may contain one or more suspect products.
‡N06 psychoanaleptics: antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, and anti-dementia drugs.

Table 3: Top 10 groups of suspect health products most commonly reported in 2010 for children 12 to 18 years old, by Anatomical Therapeutic Chemical (ATC) group*

Health product (ATC group)	No. (%) of times reported†
Psychoanaleptics‡ (N06)	69 (20.0)
Immunosuppressants (L04)	60 (17.4)
Sex hormones and modulators of the genital system (G03)	30 (8.7)
Antibacterials for systemic use (J01)	20 (5.8)
Analgesics (N02)	20 (5.8)
Antineoplastic agents (L01)	14 (4.1)
Psycholeptics‡ (N05)	12 (3.5)
Antiepileptics (N03)	9 (2.6)
Anti-acne preparations for topical use (D10)	7 (2.0)
Other nervous system drugs (N07)	6 (1.7)

*Solicited reports or organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) may affect the total number of ARs reported for specific products or product types.
†One case may contain one or more suspect products.
‡N05 psycholeptics: antipsychotics, anxiolytics, hypnotics and sedatives; N06 psychoanaleptics: antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, and anti-dementia drugs.

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.

Health Canada Santé Canada

Canada Vigilance Adverse Reaction Reporting Form

Report of suspected adverse reactions to marketed health products in Canada

See instructions and information on adverse reaction reporting and confidentiality at http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php.
Complete all mandatory items, marked by a *, and provide as much information as possible for the remaining items. PROTECTED WHEN COMPLETED – B**

A. Patient Information

1. Identifier

2. Age	3. Sex*	4. Height	5. Weight
☐ Years ☐ Months	☐ Male ☐ Female	_____ cm _____ feet	_____ kg _____ lbs

B. Adverse Reaction

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

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

2. Reaction date (yyyy-mm-dd)

3. Report date (yyyy-mm-dd)

4. Describe reaction or problem*

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

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

C. Suspected Health Product(s)

1. Name*, strength and manufacturer (if known)

#1

#2

2. Dose, frequency and route used

#1 | #2

3. Therapy dates (or duration)

#1 From (yyyy-mm-dd) - To (yyyy-mm-dd) | #2 From (yyyy-mm-dd) - To (yyyy-mm-dd)

4. Indication for use

#1 | #2

5. Reaction abated after use stopped or dose reduced

#1 ☐ Yes ☐ No ☐ Does not apply | #2 ☐ Yes ☐ No ☐ Does not apply

6. Lot #

#1

#2

7. Expiration

#1 (yyyy-mm-dd)

#2 (yyyy-mm-dd)

8. Reaction reappeared after reintroduction

#1 ☐ Yes ☐ No ☐ Does not apply | #2 ☐ Yes ☐ No ☐ Does not apply

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

10. Treatment of reaction, including dates (yyyy-mm-dd)

D. Reporter Information

1. Name*, occupation, address, telephone number*

2. Health professional?	3. Reported to manufacturer?
☐ Yes ☐ No	☐ Yes ☐ No

** As per the Treasury Board of Canada Secretariat Government Security Policy.

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Canada

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Did you know? DSEN and pediatric projects

The Drug Safety and Effectiveness Network (DSEN) was established by the Canadian Institutes of Health Research in partnership with Health Canada and in collaboration with stakeholders from across Canada.

The key objectives for DSEN are:

- to increase the evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers and patients; and
- to increase capacity within Canada to undertake high-quality post-market research in the area of drug safety and effectiveness.

One of the several funded pediatric projects aims to study pediatric prescribing rates of second-generation antipsychotics (SGAs). The objective is to develop a standardized procedure for the safe monitoring of these medications in children and youth. More information is available at http://webapps.cihr-irsc.gc.ca/cfdd/db_search?p_language=E&p_competition=200910DSA

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Aug. 23, 2011 – Nov. 22, 2011)

Date*	Product	Subject
Nov 16	CooperVision contact lenses	Recall: presence of a residue on lenses for certain lots
Nov 9 & 14	Avastin (bevacizumab)	Higher incidence of ovarian failure in premenopausal women
Nov 7	Fluoroquinolone antibiotics	Risk of increased muscle weakness for patients with myasthenia gravis
Nov 3 & 8	Pradax (dabigatran) and Plavix (clopidogrel)	Brand name confusion
Nov 2	Colgate Motion Electric Toothbrush	Recall: reports of toothbrush exploding
Oct 25 & 28	Xigris (drotrecogin alfa)	Product withdrawal
Oct 25	Brewer's Yeast tablets	Recall: presence of an undeclared milk allergen
Oct 21 & 24	Strattera (atomoxetine)	Association with increased blood pressure and increased heart rate
Oct 13	Citalopram	Review of dose-related heart risk
Sept 22	Plavix (clopidogrel)	New recommendations for use with proton-pump inhibitors
Sept 19 & 21	Trasylol (aprotinin)	Important new safety information
Sept 12	HIV home test kits	Unlicensed products
Sept 8	Gonadotropin-releasing hormone agonists	Heart-related risk in men treated for prostate cancer
Sept 1	Bi Yan Pian	Recall: excessive amount of mercury
Aug 29	Donor semen	Reminder of potential dangers of using donor semen from questionable sources
Aug 26 & 30	Sprycel (dasatinib)	Reports of pulmonary arterial hypertension
Aug 22	Central vascular access devices	Complications of catheter pinch-off
Aug 15	Uromitexan (mesna)	Association of the multi-dose vials with fatal gasping syndrome in neonates and infants
July 5	SynchroMed II implantable drug-infusion pumps	Update on battery performance of model 8637
Aug 23 to Nov 22	Foreign products	12 Foreign Product Alerts (FPAs) were posted on the Health Canada Web site during this period; FPAs are available online (www.hc-sc.gc.ca/ahc-asc/media/index-eng.php) or upon request

Advisories are available at www.health.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date on Health Canada's Web site.

Canadian Adverse Reaction Newsletter

Health Canada
Marketed Health Products Directorate
AL 0701D
Ottawa ON K1A 0K9
Tel: 613 954-6522
Fax: 613 952-7738

Editorial Team

Patricia Carruthers-Czyzewski, BScPhm, MSc (Editor-in-Chief)
Jared Cousins, BSP
Christianne Scott, BPharm, MBA
Hoa Ly, BSc
Emir Al-Khalili, BA, BScPhm
Myriam Rivas, RPharm, BSc, MQA
Sophie Bourbonnais, BScPht

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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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Minocycline: drug-induced lupus erythematosus and autoimmune hepatitis in adolescents

Key points

- Long-term use of minocycline, an antibiotic widely used off label for the treatment of acne, has been associated with drug-induced lupus erythematosus and autoimmune hepatitis.
- Since 2004, Health Canada received 7 reports of drug-induced lupus erythematosus or autoimmune hepatitis suspected of being associated with minocycline in adolescents.
- If minocycline-induced autoimmune hepatitis is unrecognized and drug exposure continues, hepatic fibrosis and chronic liver disease may develop.

Minocycline is a second-generation tetracycline that exhibits both antibacterial and anti-inflammatory properties.[1] In Canada, minocycline (first approved in 1969 under the trade name Minocin) is currently marketed by several manufacturers and is indicated for the treatment of various infections.[2]

Because the pathogenesis of acne can include bacterial proliferation (*Propionibacterium acnes*) and inflammation, oral antibiotics such as tetracyclines are frequently prescribed for the treatment of moderate to severe acne. Response to oral antibiotics is usually seen after at least 6 weeks of therapy, and treatment can last for several months.[3]

The occurrence of autoimmune disorders, such as lupus erythematosus and autoimmune hepatitis, has been associated with the use of a number of health products, including minocycline.[4–6] When these disorders are associated with drug use, the underlying mechanisms are not well established. However, long-term drug use is generally involved.[4,6] One of the most common autoimmune diseases is systemic lupus erythematosus, and about 10% of these cases can be related to drug use.[5] Drug-induced lupus erythematosus can produce symptoms that include myalgia, arthralgia and serositis, as well as abnormal laboratory results such as elevated markers of inflammation and the presence of antinuclear antibodies.[5,6] Minocycline-induced autoimmune hepatitis shares many characteristics with autoimmune hepatitis, such as the presence of antinuclear and anti–smooth-muscle antibodies, elevated immunoglobulin levels and histologic features.[4]

Minocycline is generally considered a low-risk drug in the development of drug-induced lupus erythematosus.[5,6] However, there is significant overlap of clinical presentation between drug-induced lupus erythematosus and drug-induced autoimmune hepatitis associated with the long-term use of

Table 1: Summary of 7 reports of drug-induced lupus erythematosus and autoimmune hepatitis suspected of being associated with the use of minocycline for acne in adolescents submitted to Health Canada as of Sept. 30, 2011*

Case	Age/sex	Adverse reaction (AR)†	Duration of exposure	Outcome‡
1	15/F	Drug-induced lupus erythematosus	20 mo	Recovered
2	15/F	Drug-induced lupus erythematosus	5 mo	Recovered
3	16/F	Drug-induced lupus erythematosus	9 mo	Not recovered
4	17/F	Drug-induced lupus erythematosus	3 wk	Recovered
5	16/M	Autoimmune hepatitis	8 mo	Recovered
6	15/F	Autoimmune hepatitis	2 yr	Recovered
7	18/M	Autoimmune hepatitis	Unspecified	Recovered

***These data cannot be used to determine the incidence of ARs because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Reaction terms are listed according to the *Medical Dictionary for Regulatory Activities* (MedDRA).
‡At the time of reporting.

minocycline.[4,7,8] Also, minocycline-induced lupus erythematosus and autoimmune hepatitis are well documented.

As of Sept. 30, 2011, Health Canada received 4 reports of drug-induced lupus erythematosus and 3 reports of autoimmune hepatitis suspected of being associated with minocycline use in adolescents. All the adverse reactions (ARs) were serious, involved the use of minocycline for the treatment of acne and occurred between 2004 and 2009 (Table 1).

Three additional cases were reported in 2006, 2007 and 2011 but are not included in the table because a formal diagnosis of drug-induced lupus erythematosus (in the first two cases) or autoimmune hepatitis (in the third case) was not reported. The first case reported abnormal laboratory results commonly found in drug-induced lupus erythematosus (presence of antinuclear antibodies) and arthralgia in a 15-year-old girl who had been taking minocycline for 18 months. The second case, also involving a 15-year-old girl, reported the occurrence of an illness resembling systemic lupus erythematosus after 12 months of minocycline use. The third case involved a 14-year-old girl who had been taking minocycline for about 14 months; she presented with hepatitis, polyarthralgia and polyarthritis and was reported to be experiencing an autoimmune disorder.

Minocycline-induced lupus erythematosus and autoimmune hepatitis are serious ARs that can occur in healthy adolescents receiving treatment for acne. Their clinical course can often be reversed after the drug is stopped.[6] However, if minocycline-induced autoimmune hepatitis is unrecognized and drug exposure continues, hepatic fibrosis and chronic liver disease may develop.[8] Health care professionals are reminded of the risk of autoimmune disorders suspected of being associated with the long-term use of minocycline and are encouraged to report any suspected cases.

Marie-Thérèse Bawolak, PhD; Ilhemme Djelouah, RPh, BScPhm, DIS Medical Biology (University of Paris V), Health Canada

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Fentanyl and serotonin syndrome

Key points

- Fentanyl may be associated with serotonin syndrome, a life-threatening adverse reaction, when it is used concomitantly with a serotonergic agent.
- In the past 10 years, Health Canada received 5 reports in which fentanyl was used concomitantly with a serotonergic agent and was considered a suspected drug precipitating serotonin syndrome.
- Health care professionals and patients are encouraged to report to Health Canada any cases of serotonin syndrome suspected of being associated with the use of fentanyl.

Serotonin syndrome is a potentially life-threatening adverse reaction (AR) that may be prevented and treated.[1] It is often described as a clinical triad of changes in mental status, autonomic hyperactivity and neuromuscular abnormalities.[1] Not all of these findings, however, are consistently present in all patients with the disorder. According to the Hunter Serotonin Toxicity Criteria,[2] which are generally considered to be the

preferred diagnostic tool, clonus (spontaneous, inducible and ocular) is the most important sign in establishing a diagnosis.[1] Drugs that directly or indirectly increase the intrasynaptic serotonin concentration to threatening levels can induce serotonin syndrome. The syndrome typically occurs in the setting of multiple drugs affecting serotonin neurotransmission through different mechanisms.[3] Successful management of serotonin syndrome requires heightened clinical awareness for prevention, recognition and prompt treatment.[4]

Fentanyl is a synthetic opioid agonist used as an adjunct to anesthesia and for the postoperative management of pain following general surgical procedures and cesarean sections.[5] It is also indicated for the management of persistent, moderate to severe chronic pain that cannot be managed by other means[6] and for the management of breakthrough cancer-related pain.[7,8] Fentanyl is widely used in various clinical practices, with several routes of administration.[3] The parenteral product has been marketed in Canada since 1967.

Fentanyl is not known to precipitate serotonin syndrome when used alone. However, it may be associated with serotonin syndrome when used concomitantly with a serotonergic agent.[9] The mechanism through which fentanyl may precipitate serotonin syndrome is not fully understood.[3] Fentanyl belongs to the opioid analgesic class known as phenyl-piperidines (which also includes meperidine, tramadol, methadone and dextromethorphan), which are considered weak serotonin reuptake inhibitors.[3,10] However, data on fentanyl's serotonin transporter affinity are lacking.[10]

As of Sept. 30, 2011, Health Canada received 5 reports in which fentanyl was used concomitantly with a serotonergic agent and was considered a suspected drug precipitating serotonin syndrome (Table 1). All of the cases occurred within the past 10 years. One of these cases was fatal. Ten reports, including 1 of the 5 submitted to Health Canada,[11] have been published.[3,9,11–17] Eight were published in the past 4 years.[3,9,11,12,15–17] However, no studies on the topic were found in the literature.

There are many clinical situations when an individual could be exposed to a serotonergic agent and fentanyl concomitantly, and these may precipitate a potentially life-threatening serotonin syndrome.[3,14] Health Canada is reviewing the available evidence on the association of fentanyl and serotonin syndrome and will communicate any new safety information or action resulting from its review, if indicated. Health care professionals and patients are encouraged to report to Health Canada any cases of serotonin syndrome suspected of being associated with the use of fentanyl.

Table 1: Summary of the 5 reports in which fentanyl was used concomitantly with a serotonergic agent and was considered a suspected drug precipitating serotonin syndrome submitted to Health Canada as of Sept. 30, 2011*

Case	Age/ sex	Route of fentanyl administration	Indication	Outcome	Concomitant medications with serotonergic effects†
1[11]	49/F	Intravenous	Anesthesia: cardiac surgery	Recovered	Paroxetine, fluvoxamine, meperidine, methylene blue
2	38/F	Transdermal patch	Analgesia: chronic pain syndrome	Unknown	Sertraline
3	51/M	Transdermal patch	Analgesia: back pain	Recovered	Venlafaxine
4	27/M	Transdermal patch	Unknown	Recovered	Venlafaxine
5	74/F	Unknown	Unknown	Died	Paroxetine

***These data cannot be used to determine the incidence of ARs because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Other concomitant agents not typically known to produce serotonergic activity have not been included.

Stephanie Ferrand, MD, Health Canada

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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Nov. 23, 2011 – Feb. 27, 2012)

Date*	Product	Subject
Feb 27	Gilenya (fingolimod)	Safety being reviewed by Health Canada
Feb 24	Miracle Mineral Solution and Miracle Mineral Supplement	Updated list of Web sites selling the unauthorized products
Feb 23	Unauthorized health products	Seizure of potentially dangerous products from The Love Shop retail outlets in Ontario
Feb 15	Miracle Mineral Solution and Miracle Mineral Supplement	Risk of serious health problems
Feb 13 & 15	Caprelsa (vandetanib)	Serious risk of abnormal heart rhythm
Feb 7	Non-invasive ventilation devices	Risk of being used as life-supporting ventilators
Jan 26	Doribax (doripenem for injection)	Higher mortality rate and lower clinical cure rate during a comparative clinical trial
Jan 26	Velcade (bortezomib)	Fatal if given intrathecally
Jan 25 & 30	Celexa (citalopram)	Association with abnormal heart rhythms
Jan 19	Champix (varenicline tartrate)	Updated safety information with respect to cardiovascular safety
Jan 19	Weight-loss health products	Important safety reminder
Jan 18 & 23	Rasilez (aliskiren) and Rasilez HCT (aliskiren/hydrochlorothiazide)	Potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes
Jan 13	Duet TRS loading units	Urgent recall: contraindication for thoracic use
Jan 13	Excedrin Extra Strength Caplets and Excedrin Tension Headache Caplets	Recall: possible mixing of different products in the same bottle
Dec 29	Compliments Muscle and Back Pain Relief Regular Strength	Labelling error may pose serious risks to children
Dec 23	Bivona Neonatal, Pediatric and Flextend Tracheostomy Tubes	Urgent recall of certain lot numbers
Dec 22 & 23	EpiPen and EpiPen Jr. Auto-Injectors	Information on correct usage
Dec 22	Rasilez (aliskiren)	Safety being reviewed by Health Canada
Dec 19	Bisphosphonates	Small but increased risk of unusual fractures of thigh bone
Dec 5 & 8	Multaq (dronedarone)	Important revisions to product monograph
Dec 5	Yasmin and Yaz (drospirenone)	Updated information on increased risk of blood clots
Dec 2 & Jan 23	Unauthorized health products	Updated list of products removed from sale in Burnaby and Richmond stores due to possible serious health risks
Dec 2 & 7	Avastin (bevacizumab)	Cases of severe eye inflammation leading to blindness following use in the eye
Dec 1	Ursodiol (ursodeoxycholic acid, UDCA)	High dose associated with serious liver side effects
Nov 30	Stiff One Hard 169	Recall: presence of undeclared prescription medication
Nov 30 & Dec 5	Sublinox (zolpidem tartrate)	Association with complex sleep behaviours
Nov 29	Avastin (bevacizumab)	Approval suspended for use in the treatment of metastatic breast cancer
Nov 23 to Feb 27	Foreign products	8 Foreign Product Alerts (FPAs) were posted on the Health Canada Web site during this period; FPAs are available online (www.hc-sc.gc.ca/ahc-asc/media/index-eng.php) or upon request

Advisories are available at www.health.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date on Health Canada's Web site.

Canadian Adverse Reaction Newsletter

Health Canada
Marketed Health Products Directorate
AL 0701D
Ottawa ON K1A 0K9
Tel: 613 954-6522
Fax: 613 952-7738

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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

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

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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.