TERATOGEN INFORMATION SERVICE FOR PHARMACISTS: A PILOT STUDY

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ABSTRACT

We report on the first Helpline for pharmacists dealing with the safety of medications in pregnancy and during breastfeeding. Pharmacists from all parts of Canada participated in this pilot, receiving guidance in approximately 90% of cases. There were 472 inquiries relating to 598 products with regards to safety in pregnancy and 197 calls relating to 249 products regarding exposure in breastfeeding. All callers who were surveyed found the service helpful in counseling both patients and physicians.

Key Words: *Teratogens, pregnancy, pharmacists, drug information*

A recent study from Norway ranked pharmacists only second to physicians amongst health care providers from whom patients seek advice regarding risk and safety issues of medications during pregnancy. Out of the 1373 women polled, 48.9% had used their pharmacist and 78% had inquired from their doctor.[1] In a survey completed by 414 pharmacists in France, when it came to medication started before pregnancy, 57% of the participants stated that they had recommended discontinuation of the medication. An over cautious attitude was noted among 99% of the respondents. When asked if they have sufficient information with regard to safety of medications in pregnancy, 90% answered "No". The majority of the pharmacists (97%) were interested in an information service available to help them counsel pregnant women.[2]

Several surveys have commonly shown that the perception of risk of medications during pregnancy is heightened by both pregnant women and their health care providers, including pharmacists.[1,3,4] The heightened perception of risk can lead to several dilemmas, such as, depriving women of the benefits of safe medications, reluctance in taking needed medication, suboptimal dosing, or may lead to unnecessary termination of pregnancy.[3,5] There is evidence to show that with proper information provided to pregnant women, the above concerns may be prevented.[6-8] Pharmacists play a critical role in providing accurate information to assist women's decision on whether to stop, continue or initiate treatment during pregnancy.

The Motherisk Information Line was established in 1985 and is located in Toronto, Ontario, Canada as a teratogen information phone service. It provides information about the risk or safety of exposures to prescription and over-the-counter (OTC) drugs, herbal products, chemicals, radiation, chronic diseases and infections during pregnancy and while nursing. Trained counselors answer calls from pregnant women or their partners as well as from health care professionals including physicians, nurses, midwives, pharmacists, genetic counselors, dietitians and nutritionists. Detailed information about the program has been published.[9]

On November 1, 2009, a unique pilot Motherisk-Shoppers Drug Mart Pharmacist Helpline (Pharmacist Helpline) was launched with a new toll-free number. The project arose from the need to cut down the waiting time in responding to calls from the pharmacists and hopefully, to encourage them to utilize this service. Supported by Shoppers Drug Mart (SDM), the largest retail pharmacy in Canada, the nine month pilot project aimed at probing the information needs of SDM

pharmacists and to provide data for Shoppers pharmacists to counsel their customers. The aim of this report is to provide information on the geographic distribution of the callers, the type of calls received and the rationale for the calls.

METHODS

Calls from pharmacists, pharmacist's assistants, technicians, and students calling on behalf of the pharmacist, received from the 1st of November 2009 until the 31st of July 2010, through the Pharmacist Helpline were included. Calls from other health care professionals, and women who were either pregnant or breastfeeding were excluded. Each call was documented in a standardized pharmacist intake form, which included the following data: name of caller, occupation, phone number, name of product(s), dosage, route, duration, reason for prescription, and if known, the gestational age of patient for pregnancy inquiries, and age of infant /toddler for lactation inquiries were also obtained. Geographical distribution of calls was based on the area code of the phone number provided. The type of medication was classified according to its common or actual usage, if known. For a better understanding of the rationale for the inquiry in pregnancy, medication and exposure inquiries were classified based on the US Food and Drug Administration (FDA) risk category (Table 1)[10] using Micromedex®.[11] When medications were not categorized by the US FDA, Briggs' classification,[10] which follows the FDA guideline was used. Pharmacologic products not classified, exposures that were not a pharmaceutical agent, and herbal products were labeled as N (not classified), NA (not applicable for classification), and H (herbal), respectively. If a product had multiple active ingredients, classification was based on the ingredient that had more concern. For example, Robitussin Total Cough, Cold and Flu with acetaminophen (B), dextromethorphan (C), and pseudoephedrine (C) would be classified as C. When assigning risk category in pregnancy for drugs with multiple ingredients, the following hierarchal system was used: X > D > N > C > B> A.

TABLE 1 FDA Risk Category[10]

US FDA RISK CATEGORY	DESCRIPTION
CATEGORY A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
CATEGORY B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
CATEGORY C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
CATEGORY D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
CATEGORY X	Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Medication and exposure inquiries, with regards to risk and safety in breastfeeding were classified based on Hale's lactation risk category (Table 2).[12] Medications, herbal products and exposures that were not found in Hales book, were classified as LN (pharmacologic product not classified). LNA (exposures that are not a pharmaceutical agent, not applicable for Hale's lactation classification), and LH (herbal products not classified). If a product had multiple active ingredients, classification was based on the ingredient that had more concern. For example, Diclectin active ingredients are doxylamine (L4) and pyridoxine (L2). This medication was classified as L4. When assigning risk category in breastfeeding for drugs with multiple ingredients, the following hierarchal system was used: L5 > L4 > LN > L3 > L2> L1.

At the end of each call, the majority of the pharmacists were asked whether they found the Motherisk-Shoppers Pharmacists Helpline helpful and whether the provided information assisted in counseling their customers.

TABLE 2 Thomas W. Hale's Lactation Risk Category [12]

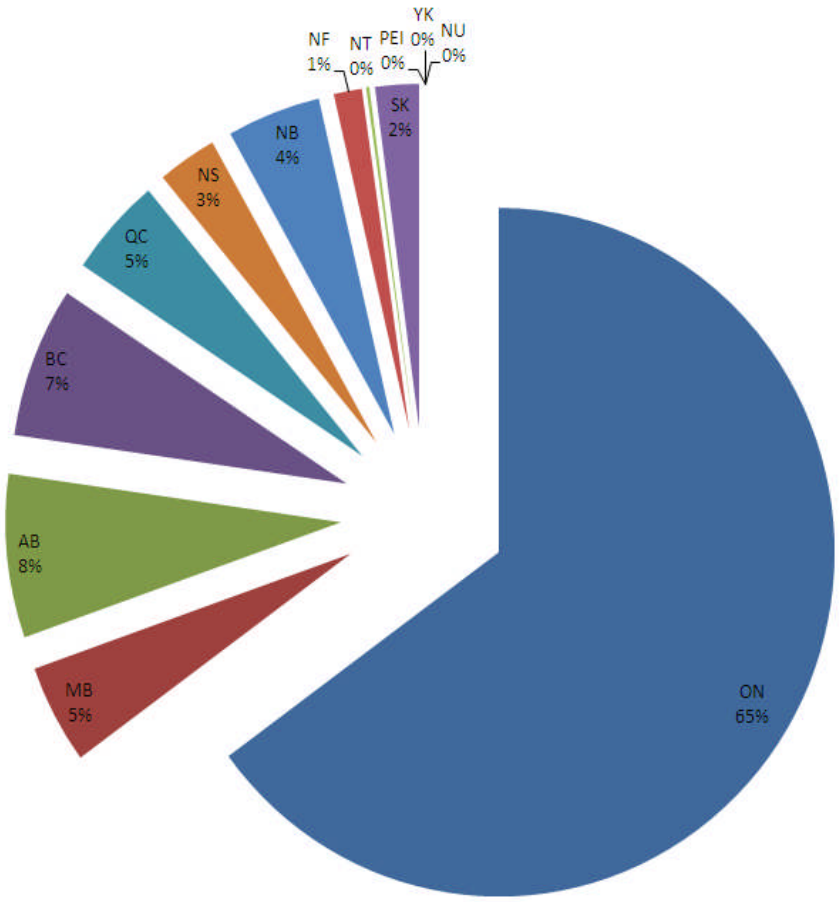
RISK CATEGORY	DESCRIPTION
L1 SAFEST	Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.
L2 SAFER	Drug which has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. And/or, the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.
L3 MODERATELY SAFE	There are no controlled studies in breastfeeding women, however, the risk of untoward effects to a breastfed infant is possible; or, controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. (New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be.)
L4 POSSIBLY HAZARDOUS	There is positive evidence of risk to a breastfed infant or to breastmilk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
L5 CONTRAINDICATED	Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

RESULTS

Geographic Distribution of Callers from Shoppers Drug Mart

The Pharmacist Helpline received a total of 653 calls from 403 pharmacists and associates during the nine month pilot period. Three hundred thirty (26%) of 1,239 SDM stores participated. The majority of calls came from Ontario (65%), followed by Alberta (8%), British Columbia (7%), Manitoba (5%), Quebec (5%), New Brunswick (4%), Nova Scotia (3%), Saskatchewan (2%) and Newfoundland and Labrador (1%) (see Figure 1).

FIG. 1 Percentage of calls based on geographical distribution

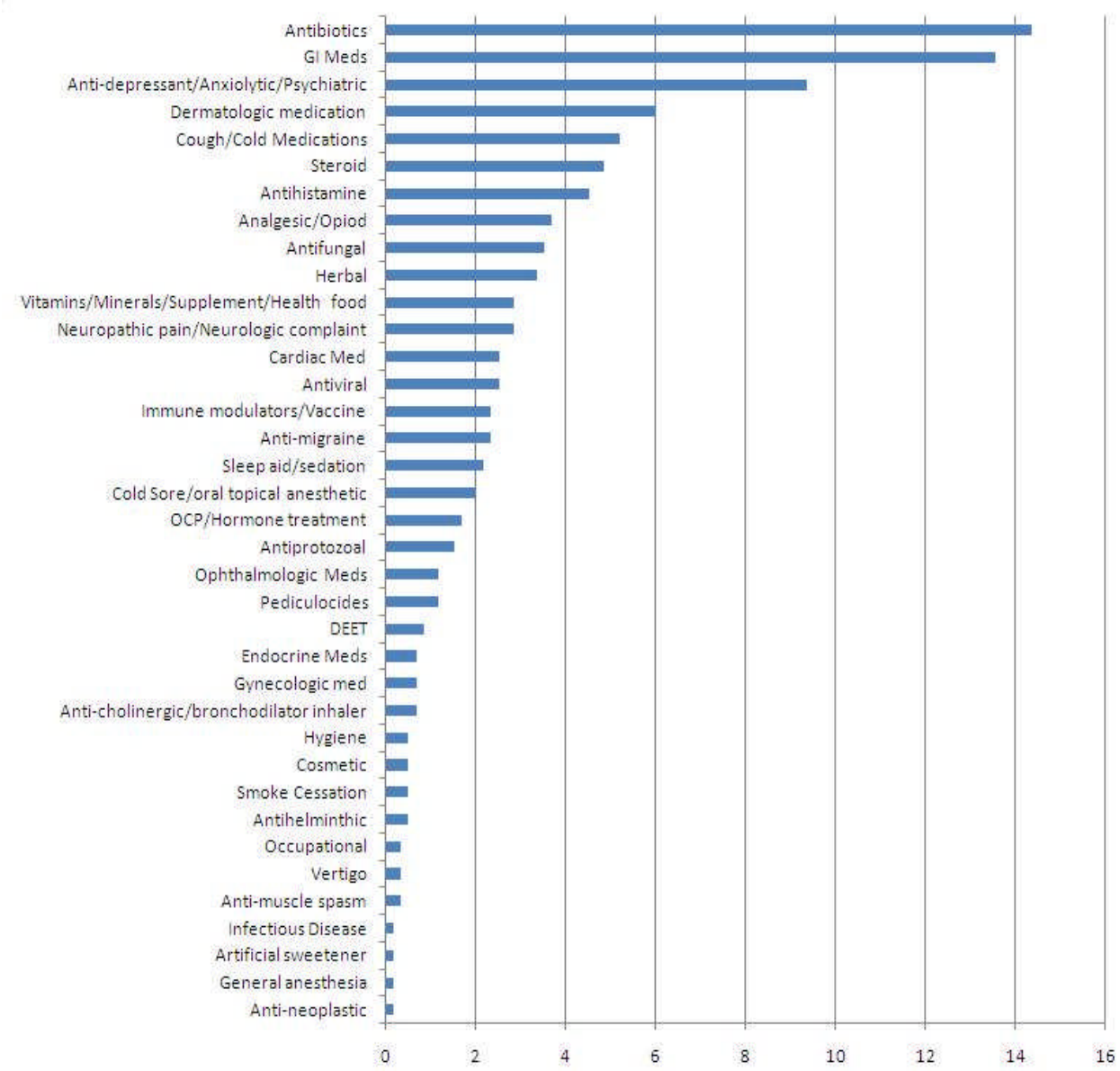


Medications in Pregnancy

Type of medications

There were 472 calls inquiring about 598 products with regards to safety in pregnancy from pharmacists. The 10 most common product inquiries were: antibiotics (14.3%); gastrointestinal (GI) medications (13.5%); psychiatric medications (9.3%); dermatologic medications (6%); cough & cold medications (5.2%); steroid containing products (4.8%); antihistamine (4.5%); pain reliever (3.6%); antifungal (3.5%) and herbal (3.3%) (see Figure 2).

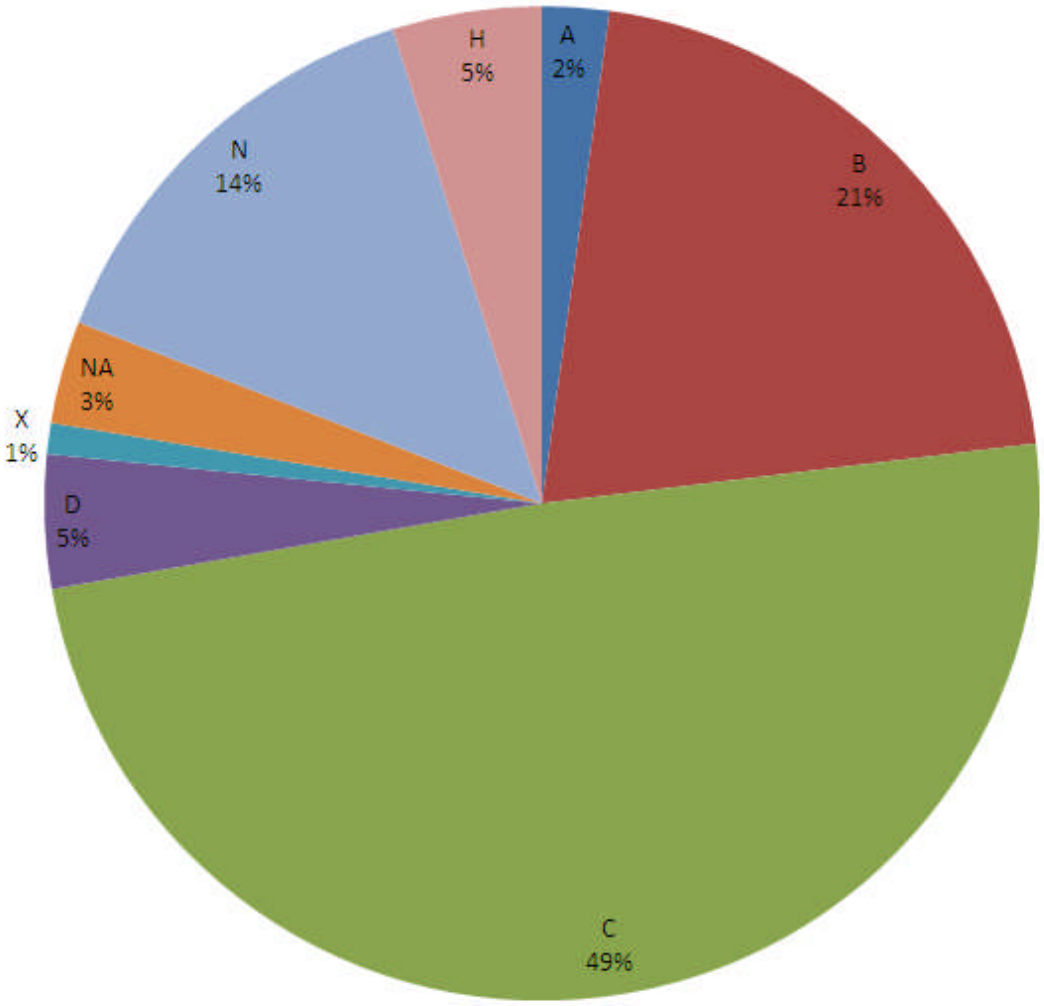
FIG. 2 Percentage of calls according to type of products in pregnancy



Risk Classification of Calls

Out of 598 products, 49% had a FDA risk C label, 21% a risk B label, 5% a risk D label, 2% a risk A label and 1% a risk X label (see Figure 3). Fourteen percent of the products queried had unknown classification. Herbal product inquiries comprised 5% of the calls, whereas, 3% were non-medicinal products such as insect repellants, artificial sweeteners, products for hygiene and cosmetics, occupational exposures and infectious diseases. Eight out of the 16 calls about products categorized as risk A were questions on proper dosage of medications rather than safety data. Four of the six products in risk category X were oral contraceptive medications. The other ones were queries on elimination time for isotretinoin in a woman who is planning pregnancy and the safety of triazolam.

FIG. 3 Percentage of products inquired classified based on FDA risk category



There were 85 products that had no FDA risk category, of which only one product, topical retinyl palmitate that has teratogenic potential. Fifty five percent (47/85) were products with limited systemic absorption such as topicals, aerosols and lozenges. Concerns or possible concerns comprised 35% (213/598) of the product inquiries (see Table 3).

In 93.8% (443/472) of the calls, the Pharmacist Helpline provided guidance (such as safe to use in pregnancy, avoid after 32 weeks of gestation or avoid in first trimester) on 564 product exposure inquiries. There were 34 product inquiries, for which the data was either limited or unavailable, and the pharmacists were so advised.

TABLE 3 Number of calls on products of concern/possible concern in pregnancy

CLASS/NAME OF PRODUCT	NUMBER OF CALLS	CLASS/NAME OF PRODUCT	NUMBER OF CALLS
Accutane/Vitamin A derivative	4	Non-Steroidal Anti-inflammatory Drug (NSAID)	7
Amantadine	1	Opioids	15
Benzodiazepine	9	Oral Contraceptives/Hormonal treatment	10
Beta Blockers	10	Pizotifen	1
Betahistine	2	Pramipexole	1
Calcium Channel blockers	6	Pregabalin	3
Clonidine	1	Procyclidine	1
Dextroamphetamine	1	Propylthiouracil	2
Fluconazole	8	Ropinirole	1
Fluoroquinolones	7	Seizure Meds	4
Imiquimod	1	Selective Serotonin/Norepinephrine Reuptake Inhibitor (SSRI/SNRI)	33
Lithium	1	Spirinolactone	1
Malarone	2	Steroids	40
Melatonin	2	Tizanidine	1
Methylphenidate	1	Tricyclic Anti-depressant (TCA)	5
Minocycline	1	Trimethoprim/Sulfamethoxazole	6
Modafinil	2	Varenicline	3
Niacin	1	Zoprasidone	1
Nitrofurantoin	18		

Breastfeeding

Type of medications

The pharmacists and their associates made 197 calls and inquired about 249 products and exposures related to breastfeeding. The 10 common products and exposure inquiries were: antibiotics (15.6%); GI medications (12%); psychiatric medications (10.8%); NSAIDs/opiate analgesics (8.4%); antihistamine (7.2%); and steroid/ immune modulators (6.4%); cough and cold remedies (5.6%); gynecological medications including oral contraceptive pills (4.4%); dermatologic medications (3.6%) and antiviral (3.2%) (see Figure 4).

FIG. 4 Percentage of calls according to type of products in breastfeeding

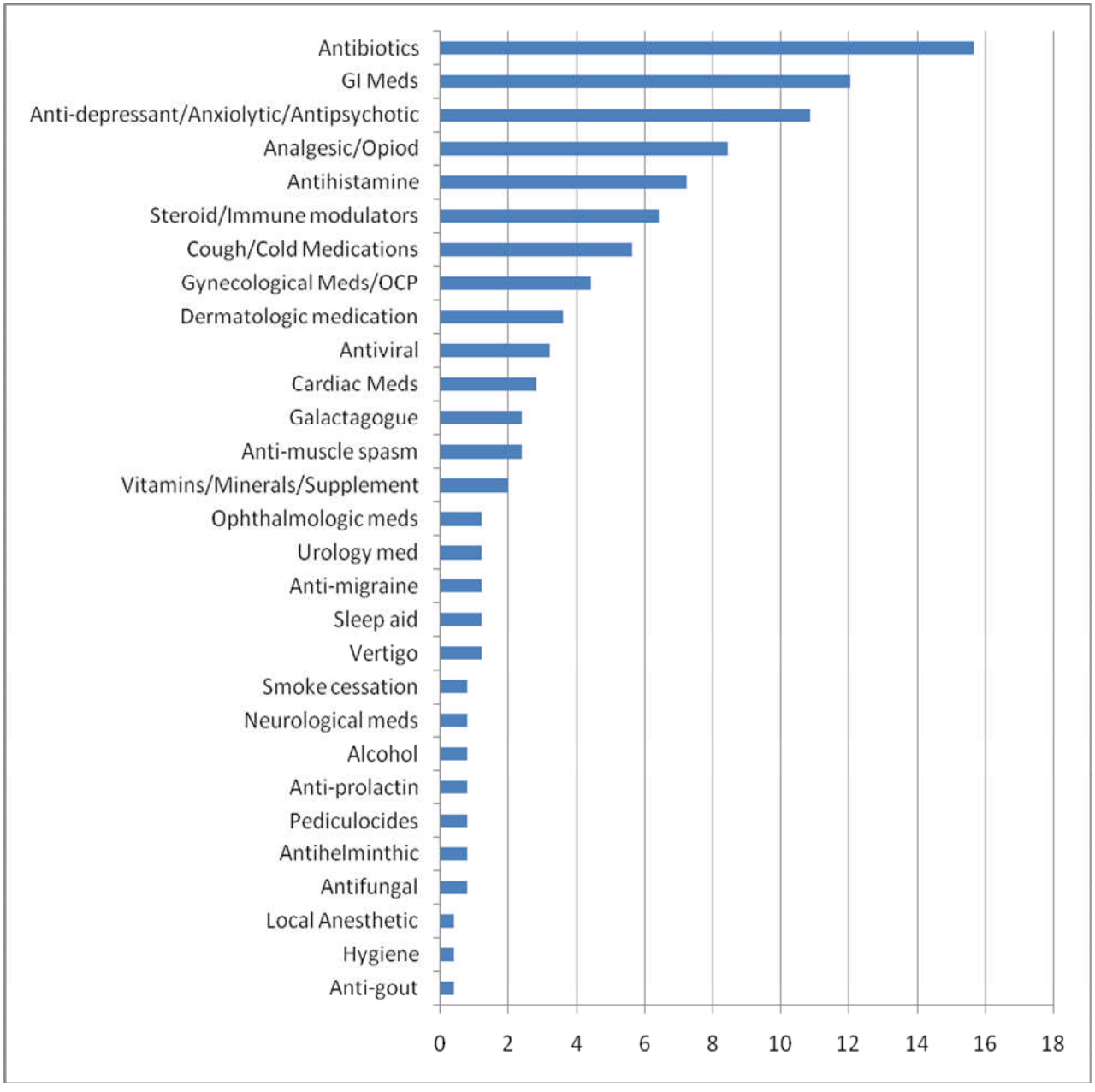
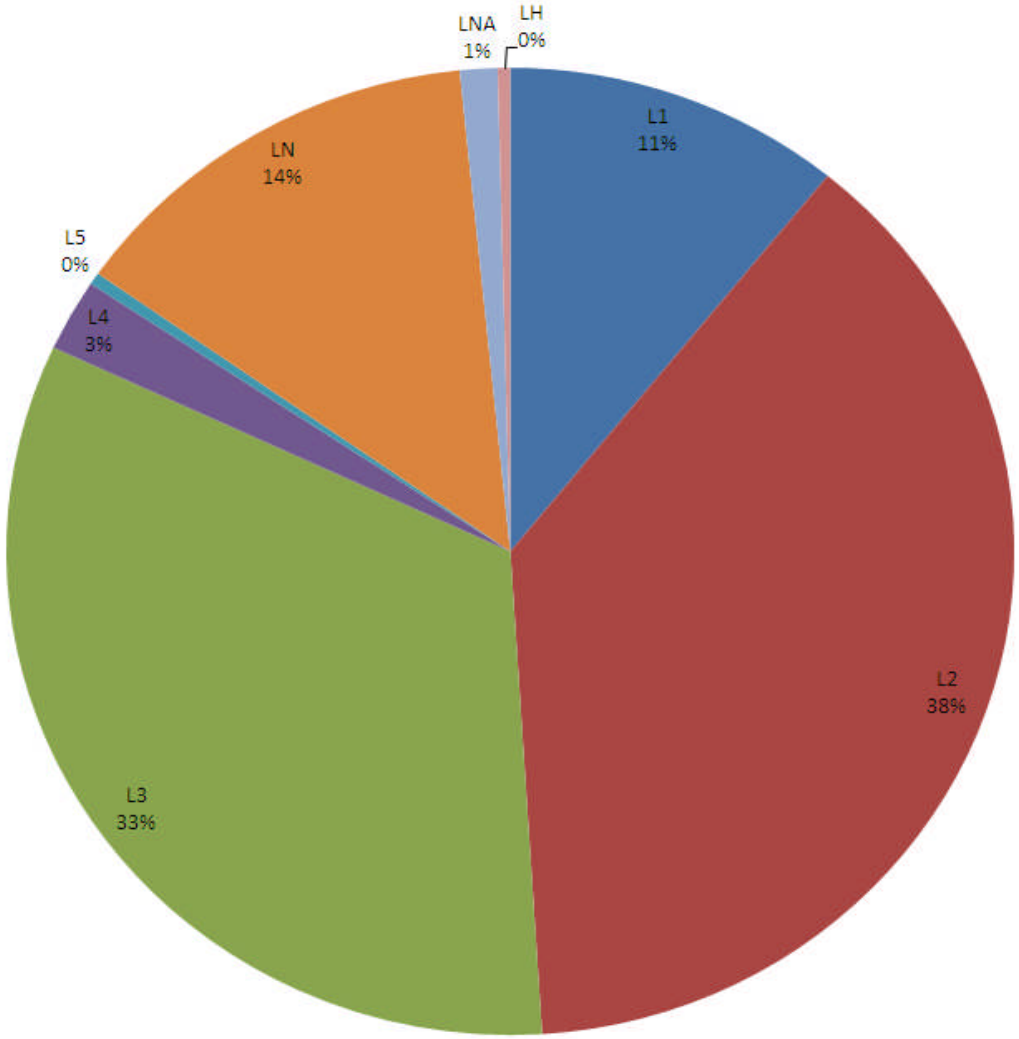


FIG. 5 Percentage of products inquired classified based on Dr. Hale's lactation risk category



Risk Classification of Calls

Out of the 249 products and exposure inquiries, 38% were classified as L2; 33% as L3; 11% as L1; 3% as L4 and 0% as L5 (see Figure 5). Products that were not classified in Hales' book comprised 14% of the inquiries. Products such as food and products for hygiene, classified as LN, made up 1% of the inquiries. Not all calls involved concerns of safety, as pharmacists sometimes called about the proper dosage of the medication. There was a call from a pharmacist who inquired about medications that can be used to suppress lactation. Cabergoline (L4) and bromocriptine (L5) were discussed accordingly. The other products classified as L4 were doxylamine found in Diclectin, nitroglycerin topical and varenicline.

Pharmacists received definitive guidance (such as safe to use while breastfeeding, or hold breastfeeding for 8 hours) in 88.8% (175/197) of calls. There were 9% (22 out of 249 products) of inquiries that may be of concern (see Table 4). Fourteen out of the 22 products of concern had insufficient data to provide risk and safety information regarding use while breastfeeding.

TABLE 4 Number of calls on products of concern/possible concern in breastfeeding

CLASS/NAME OF PRODUCT	NUMBER OF CALLS	CLASS/NAME OF PRODUCT	NUMBER OF CALLS
Atenolol	1	Melatonin	1
Betahistine	3	Meloxicam	2
Clopidogrel	1	Nitrofurantoin	1
Cyclobenzaprine	2	Perindopril	1
Cyclopentolate	1	Rizatriptan	1
Estrogen	1	Tamsulosin	2
Hydroquinone	1	Varenicline	1
Levonorgestrel	2		

Call Satisfaction

Out of 592 calls where the pharmacists were asked for their satisfaction, 100% answered that they found the line helpful. For those who were told that there are no data or limited data on the risk and safety of the product or exposure, they found that such information would guide them on what to inform customers or physicians. Knowing that there are no studies or limited studies, helps confirm their own drug safety database.

DISCUSSION

In Canada, Garriguet reported the pattern of medication use among pregnant women from 1994 – 2003.[13] A rise in the use of non-prescription medication during pregnancy from 27% to 33% was noted. The top 3 users in 2001-2002 were Prince Edward Island (45%), Newfoundland-Labrador (41%) and Nova Scotia (41%). Ontario had the lowest rate at 29%. The use of prescription medication remained relatively unchanged for the 10 year period at 26% in this group of women. In 2001-2002, Nova Scotia (37%), Newfoundland (36%) and New Brunswick (35%) were the top three users for prescription medication, while Ontario (22%) had the lowest rate. The most common medications used during pregnancy were pain relievers (42%), stomach remedies (11%), cough and cold remedies (10%) and antibiotics (8.5%). Surveys on medications used during pregnancy revealed about 15.8 - 36.4% were classified as US FDA category C, 2 - 6.4% category D and about 1- 4% category X.[14-17] Given these data, it is fairly common for pharmacists to encounter prescriptions wherein they have concerns on the safety of a medication prescribed during pregnancy and breastfeeding. To our knowledge, this is the first time the description of medications and risk category that pharmacists inquire about from a teratogen information service has been reported.

During the study period, about 26.6% of the SDM stores utilized the line. This relatively low rate might be due to the pharmacists relying on other sources of information such as their local teratogen information service, provincial drug information line, drug monograph, computer drug safety database, and resource books. It may also be partly due to lack of awareness of the new service and perhaps lack of time to inquire on behalf of patients. Importantly, it takes time for all stores to become aware of a specialized service such as this one. From November 1, 2009 to February 28, 2010, the SDM Pharmacist Helpline received about 321 SDM pharmacist calls. During the same time-period, there were 367 pharmacist calls received on the general Motherisk line, the majority of which were pharmacists from other drug store chains. According to the Canadian Association of Chain Drug Stores 2010 report, there were about 8,500 retail pharmacies in Canada.[18] Shoppers Drug Mart had about 1200

stores.[19] Comparing the relative volume of pharmacist calls within the 3 month period between the general Motherisk line (367 pharmacist calls/7300 pharmacy retail store excluding SDM =5 %) and the SDM Pharmacist Helpline (321 SDM pharmacist calls/1200 SDM retail store = 26.7%), there was at least five times more calls received from SDM pharmacists. The higher rate of calls among the SDM pharmacists was partly due to the promotions within the SDM store chain and two lectures provided by Motherisk to their pharmacists during the pre-launching of the Pharmacist Helpline.

The majority of calls came from stores within the province of Ontario where Motherisk is located, thus accounting for 65% of the total calls. Part of the reason for the large volume of calls from Ontario is due to the fact that SDM has 611 of its 1239 stores,[19] about 50%, located in Ontario and probably the majority of pharmacists in Ontario were already familiar with the service. Provinces such as Manitoba, New Brunswick, Nova Scotia, Saskatchewan and Newfoundland have relatively few SDM stores in their area and a relatively smaller population (see Table 5).[19,20]

Antibiotics, medications for gastrointestinal symptoms, and psychiatric medications were the most common inquiry for use in pregnancy by pharmacists during the 9-month period. The majority of calls were on products classified by the US FDA as category risk C (49%), 21% as category B, and 14% of calls were on products that are not classified. Risk categories B and C, along with the unclassified products, comprise the majority of the drugs on the market. Since these 3 categories imply risk that is somewhat equivocal, it makes sense that pharmacists needed more guidance with these products. Despite the labeling of US FDA category A, we had 16 product inquiries, 50% of the inquiries were on the proper dosage of the medication rather than on the safety data. Four of the six products in risk X were oral contraceptive medications, which were either due to contraception failure or for use as luteal phase support during pregnancy. Of the 85 products that were not classified by FDA, only one had teratogen potential while about half were products with limited systemic absorption or low systemic dose such as topical, aerosols and lozenges.

Wen and colleagues reported that one in every five women uses FDA C, D, and X drugs at least once during her pregnancy. In their report, the most common prescription drugs in pregnancy under categories C, D and X were antiasthmatics, antibiotics, NSAIDS, anxiolytics, antidepressants, and oral contraceptives.[15] We observed similar trends. We classified the steroid containing antiasthmatic medications under steroids since this is the primary concern of the pharmacists. More than half of the medications used by pregnant women for gastrointestinal symptoms, and for cold and cough are either over the counter or have no FDA risk category and would not have been noted by Wen et al. However, Garriguet observed the same high use of these products among pregnant women.[13] Unlike the other reports, we found that the use of topical dermatologic products were also frequent among pregnant women.

Addis et al. compared 1,032 drugs using 3 classification systems: US FDA, the Australian Drug Evaluation Committee (ADEC) and the Swedish Catalogue of Approved Drugs (FASS). The group found only 26% of the 236 drugs common to all 3 systems that were placed in the same risk category.[21] Furthermore, while 26% of the drugs in Sweden are classified as category A, only 0.7% of the drugs were in the FDA classification. This shows the disparity towards risk categorization of drugs in pregnancy, which may cause confusion and overestimation of risk. An example would be triazolam, which is classified as US FDA category X, but assigned to category C by the ADEC and the FASS. In counseling a pregnant woman, the pharmacist needs to keep in mind the period of gestation when the patient is taking the medication. For example, short term use in the second trimester of benzodiazepine for sleep difficulty is not a concern. In treating anxiety, the risk and benefit would always have to be weighed on an individual basis. In this scenario, if a pregnant woman is using a benzodiazepine in the first trimester, we would inform the pharmacist of the probable small potential risk of oral cleft in the first trimester.[22] If the benefit outweighs the risk, the patient would benefit from a detailed ultrasound of the fetus between 16-20 weeks gestation to rule out this defect. Use in the third trimester until near delivery time may lead to risk of neonatal withdrawal, thus the newborn needs to be monitored for withdrawal symptoms and may

need to stay in the hospital for treatment or observation. The risk category must consider the context of why a medication is prescribed to a patient and the timing of use in pregnancy. When a pharmacist warns a patient that the drug may cause harm to the fetus because it carries a category C, this may have a major impact in the decision making by the patient.

Pregnancy risk categories are suboptimal, often outdated and too superficial to account for the physiology and health care needs of pregnant women. They are rarely or too hastily revised as new information becomes available.[15] The manufacturer is rarely interested in the use of their drug in pregnancy, in an attempt to avoid legal risks. Many drugs are labeled as not to be used during pregnancy by the manufacturer and this raises concerns among women who read the product monographs believing that they were based on clinical evidence, which in a lot of cases were influenced by the current hostile medico-legal environment. In 2000, the FDA was advised by its experts and advisors to change the labeling system from "categories" to "structured narratives" which will provide the clinicians all that is known on the specific drug, even if the company does not wish to have a pregnancy indication. The changes were approved in 2009 to be enacted in 2010. Examples of this new system have been recently published.[23] In counseling, we used similar narratives instead of the FDA classification when we provided risk and safety information on a certain product.

Concerning breastfeeding, the top five frequent medication types inquired by pharmacists were antibiotics, medications for gastrointestinal symptoms, psychiatric medications, pain relievers, and antihistamines. These were the same products that were commonly used during pregnancy. In the majority of products, manufacturers placed a warning such as not to breastfeed or avoid when breastfeeding. Breastfeeding mothers are often left in a state of confusion when their health care provider encourages them to breastfeed while the product monograph informs them otherwise. For this reason, the new helpline provided important resource and further guidance. Products classified under L2, L3 and LN comprised 85% of the calls in breastfeeding. These classifications include products whose safety in breastfeeding, are not well established. In reality, the majority of medications are excreted into breast milk in insufficient quantity to cause harm to the suckling infant despite being labeled L2 and L3. In counseling, health care providers should be cautious in using the label. Instead, the relative infant dose, the pharmacokinetics of the drug and clinical data in breastfeeding should bear more weight in determining risk assessment. As an example, let's consider metronidazole. According to Hale[12], the oral and intravenous (IV) form is classified as L2, whereas the topical form is classified as L3. Reason for this discrepancy is that the literature has shown the relative safety of metronidazole in its oral and IV form, whereas no such report has been published for the gel form. However, considering the pharmacokinetics, one should expect less of the metronidazole going into the breast milk for the topical form and thus in terms of safety, the topical metronidazole would be less likely to cause harm.

In conclusion, the Pharmacist Helpline was able to provide guidance in 93.8% of pregnancy related calls and in 88.8% of breastfeeding inquiries. As expected, the majority of calls were on medications that are either not classified or whose risk classification in pregnancy and breastfeeding were ambiguous. All the pharmacists who used the line, found it helpful in counseling their patients as well as validating their own risk perception. An assessment of how this helpline has impacted the pharmacist call volume in the Motherisk general line has not been conducted. A comparison between the calls received from the Motherisk Helpline and the Shoppers Pharmacist Helpline would be of interest in determining the long term role for a health care professional helpline.

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