REGIONAL PRESCRIBING PATTERNS IN THE ASSESSMENT OF THE RESPONSE TO SAFETY WARNINGS FOR MEPERIDINE

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ABSTRACT

Background
The use of meperidine (Demerol©) as an analgesic is associated with serious adverse effects due to its metabolism to normeperidine. National safety warnings were issued in 2004/2005.

Objectives
To assess the population level and regional variation in the prescribing of meperidine and response to voluntary safety warnings in Manitoba.

Methods
A serial cross-sectional study was conducted utilizing the Manitoba Pharmacare database to determine regional patterns of use of meperidine from 2001-2011.

Results
The provincial quarterly Defined Daily Dose (DDD) rate dropped significantly from 10.8 to 7.9 DDD/1000 persons/quarter. Rate of use declined significantly in six of eleven regions ($p<0.001$) but three regions showed increased rates of use (NS). While only 4% of physicians continue to prescribe meperidine, three regions have rates of use of approximately double the provincial average.

Conclusions
Meperidine use has declined in Manitoba since the release of safety warnings. The majority of physicians no longer prescribe this agent for community use but a minority of prescribers contribute to regional pockets of higher use. These results point the way to future recommendations for quality improvement in meperidine use. Targeting future educational interventions to selected areas may be the best use of educational resources to further decrease use. Alternatively, policy changes to remove meperidine from provincial drug coverage may be a more effective strategy.

Key Words: *Meperidine, safety warnings, prescribing behaviour*

Meperidine (Demerol©) is a synthetic opioid developed in 1938 which went on to become widely prescribed.[1] Following the same path as a more recent opioid product (OxyContin©)[2] meperidine was initially touted as being more effective, less prone to abuse, and to be less addictive than other opioids.[3-5] We now know that none of these claims are correct and meperidine is actually associated with more risks and drawbacks than other opioids.[6]

Meperidine has a half-life of 2-3 hours, and a low and erratic oral bioavailability due to first pass metabolism, making oral use less effective.[7] One of the major metabolites is normeperidine, a partially active, renally excreted, neurotoxic molecule. Normeperidine has a half-

life of 14-21 hours, increasing to 34-48 hours in patients with renal insufficiency. Continuous use of meperidine thus leads to rapidly rising levels of normeperidine. Elevated normeperidine levels result in a syndrome of excitotoxicity due to its stimulatory effects. Symptoms of this toxidrome include dysphoria, agitation, muscle fasciculation, delirium, and seizures.[3,4,6,8] These neurotoxic effects are not antagonized by naloxone and may even become worse if it is administered.[9]

The risk of normeperidine toxicity increases with dose and duration of treatment. Use in patients with renal dysfunction, daily doses over 600 mg, or use for more than 48 hours is not recommended.[8-11] It is never appropriate to use meperidine for the treatment of chronic pain.[8-11]

The problems associated with the use of meperidine have been acknowledged in the academic and clinical literature for some time. Translating this knowledge into clinical practice change, however, is an ongoing process. The Institute for Safe Medication Practices (ISMP) Canada has taken steps to try to raise the profile of this issue in practice and released a bulletin in August 2004 regarding the safety of meperidine, outlining the risks associated with the use of meperidine, recommending that oral meperidine be stricken from formularies, and parenteral forms be restricted in hospitals.[6] A second ISMP bulletin was published in April 2005, reporting again on safety and normeperidine neurotoxicity. In it they reported that doses as low as 260 mg per day have been reported to cause grand mal seizures.[10]

While it is assumed that the dangers inherent to the use of meperidine are widely known, there has been relatively little study about the impact of the safety warnings on use in community and rural practice. This study examines trends in the use of meperidine across Manitoba over a ten year period to assess the impact of safety warnings on regional patterns of meperidine prescribing.

METHODS

Data Collection

Administrative healthcare data was used to conduct a serial cross-sectional study to examine trends in the use of meperidine in the community setting. Approval for this study was obtained from the University of Manitoba's Health Research Ethics Board and Manitoba Health's Health Information Privacy Committee. Administrative data were obtained from the Population Health Research Data Repository, housed at the Manitoba Centre for Health Policy (MCHP) within the University of Manitoba. The repository is unique in that it contains de-identified individual level data for the population of Manitoba from 1984 and is linkable across data sets made anonymous through a scrambled patient health information number. The repository contains records for virtually all contacts with the provincial health care system.[12]

Manitoba has a universal prescription program (Pharmacare) for all residents. Prescription claims are submitted by pharmacies and processed by the Drug Program Information Network (DPIN) electronically in real-time. The prescription data collected includes patient name, ID, prescriber ID, name of drug, drug identification number (DIN), dose strength, metric amount dispensed, and number of days supplied (as determined by pharmacist). This data is stored and submitted to MCHP annually for addition to the repository.

The Manitoba Health Registry contains information on all residents enrolled in Manitoba Health, including their last available address. From this database we were able to determine the population of each health region. This registry is updated on an ongoing basis, allowing our rate calculation to adjust for changes in the populations over time.

Data was extracted from DPIN using SAS version 9.4. Data from all claims for oral meperidine prescriptions between April 1st 2001 to June 10th 2011 of patients aged 16 years and older were extracted.

Analysis Method

Analysis was done using SAS 9.4®, Microsoft Excel 2010®, and SPSS 22®. We determined the amount of meperidine dispensed per 1000 persons per fiscal quarter across Manitoba, as well as within each of the 11 Regional Health Authorities (RHAs) within Manitoba. We also determined the percentage of licensed physicians that prescribed meperidine in each quarter.

Defined Daily Doses

The World Health Organization (WHO) has outlined a method for expressing population drug utilization using Defined Daily Doses (DDD). A DDD is defined as "the average maintenance dose of the drug when used for its major indication in adults."[13] The WHO assigned DDD value for meperidine is 400 mg, equivalent to 8 x 50 mg tablets, a day (i.e. 50 mg po q3h, a dose which would provide 24 hour analgesia).[14]

Duration

For every prescription dispensed, the quantity dispensed was divided by the DDD value to calculate the DDD units of each prescription. The duration of each prescription was thus equal to the number of DDDs supplied.

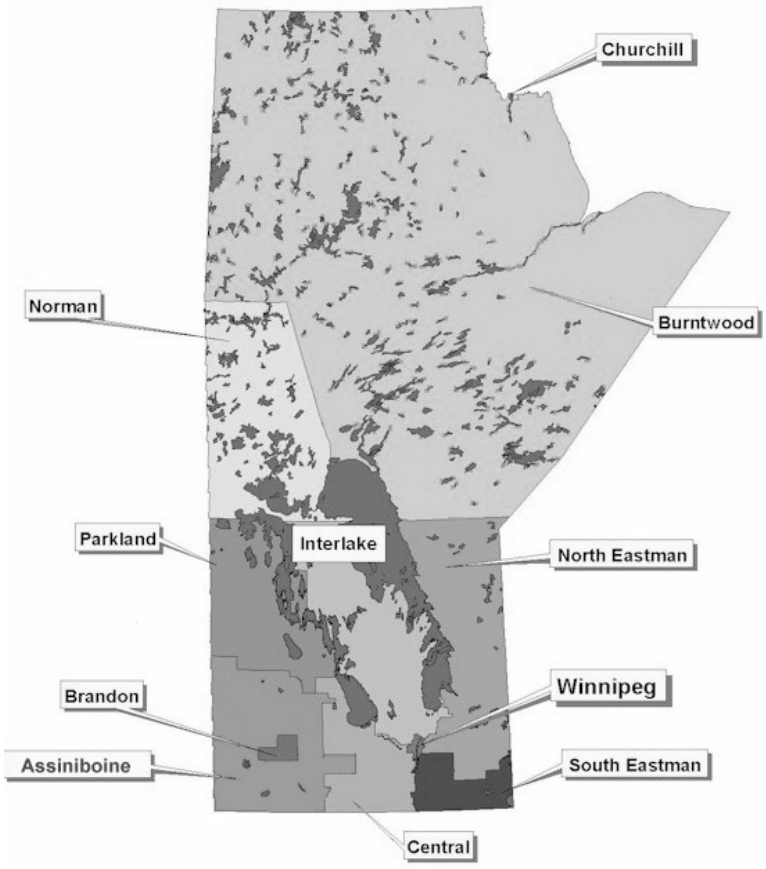
DDD Rates

Following the method recommended by the WHO, we expressed rates of use in terms of DDDs per 1000 persons.

Administrative Regions

Manitoba is divided up into a number of Regional Health Authorities (RHAs). During our study period (2001-2011) Manitoba was divided into eleven RHAs, nine of them are predominantly rural RHAs and two (Winnipeg and Brandon) urban (Figure 1). In 2012 many of these RHAs were amalgamated into five larger RHAs. The pre-2012 definitions were used when expressing our DDD rates by RHA.

FIG. 1 Map of Manitoba with pre-2012 RHA districts



Physicians Prescribing

The time trends in physician prescribing were examined by counting the number of unique physicians prescribing meperidine in each fiscal quarter. The total number of physicians was determined by the number registered by the College of Physicians and Surgeons of Manitoba.

Statistical Analysis

To examine changes over time in the data the calculated DDD's were assigned into their corresponding fiscal quarter. Prescriptions that spanned quarters had their DDDs divided on a pro-rated basis between the quarters. The regional average quarterly DDD rate from the first twelve quarters of our study period was compared to the last twelve quarters using Student's two sided t-tests. Three year averages compensate for the large variance from quarter to quarter when looking at the data at the regional level with their smaller populations. An adjusted p-value of 0.004 was used to denote significance to account for multiple comparisons (Bonferroni correction).

RESULTS

Provincial and RHA DDD rates over the first and last 3 years of our study period are shown in Table 1. Overall, at the provincial level, the DDD rate of meperidine dropped substantially in the ten year period. This significant decrease in the amount of meperidine being dispensed did not occur uniformly in all regions of the province.

TABLE 1 DDD Rates across Manitoba by RHA

Table 1. DDD Rates Across Manitoba by RHA

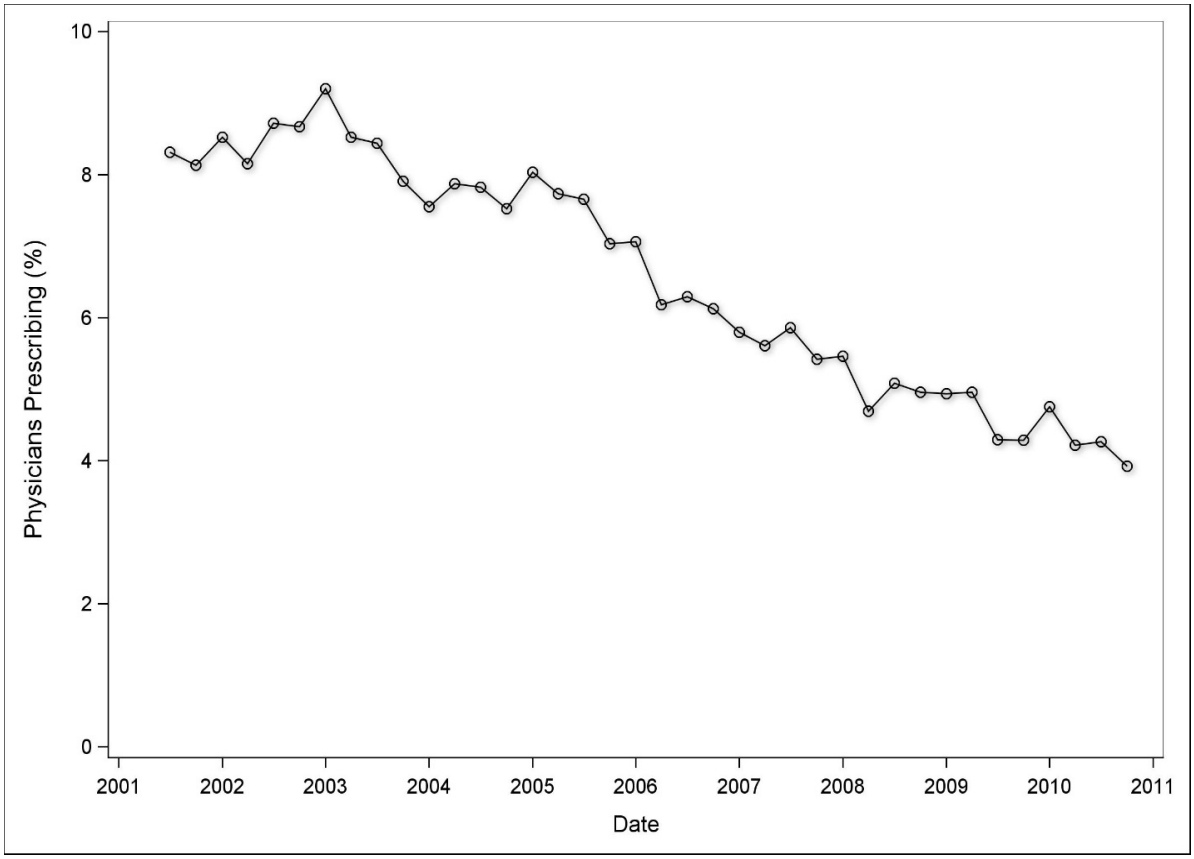
	Rural RHA's									Urban RHA's		
Average Quarterly DDD Rates†	Assiniboine	Burntwood	Central	Churchill	Interlake	N. Eastman	Nor-Man	Parkland	S. Eastman	Brandon	Winnipeg	Manitoba
2001-03 Ave	10.55	2.80	10.55	0.13	10.65	7.40	21.41	15.25	45.57	4.15	9.04	11.15
2008-10 Ave	4.83	3.27	6.86	3.05	9.17	3.95	14.79	19.14	15.43	1.79	7.81	7.93
Mean Change	-5.71	0.46	-3.69	2.92	-1.48	-3.45	-6.63	3.90	-30.13	-2.36	-1.23	-3.22
p Value	<0.001*	0.26	<0.001*	0.26	0.10	0.01	<0.001†	0.02	<0.001*	<0.001*	<0.001*	<0.001*

* Statistically significant. Bonferroni correction for multiple comparisons used, p= 0.004 was considered significant.
† Rates are in DDD/quarter/1000 persons.
DDD – Designated daily dose
RHA – Regional Health Authority

Of the 11 RHAs, eight of them showed a decrease over the ten year period with five of these regions having decreases that were considered statistically significant. Three regions had dramatic reductions in meperidine use with DDD rates dropping by half or more (Assiniboine 54%, Brandon 57% and North Eastman 47%). Three regions showed increases in meperidine, none of these increases was considered statistically significant. Churchill RHA had a very high relative increase in meperidine prescribing during this period (a 20 fold increase); but, their final rate was still well below the provincial average.

Our analysis of the proportion of physicians prescribing meperidine is shown in Figure 2. We found that the percentage of physicians who wrote at least one prescription in a quarter dropped significantly over the ten year study period. Over this same time period the number of licensed physicians in Manitoba increased marginally, rising from 4,293 in 2001 to 4484 at the end of 2010, an increase of less than 4.5%. Over the first four years of our study, approximately 8% to 9% of physicians were prescribing meperidine. After July 2005 there was a significant change in the prescribing rate, with a relatively constant decrease in physicians prescribing meperidine of 0.68% each year. By the last year of our study period, the average percent of physicians that prescribed meperidine in a given quarter was 4.1%. This represents a drop of 50% over a ten year period. In the very last quarter of our study, only 3.9% prescribed meperidine.

FIG. 2 Percentage physicians prescribing meperidine



DISCUSSION

Given the safety concerns raised by ISMP and others, it is encouraging to see that meperidine use across Manitoba declined across our ten year study period. Regional patterns were variable but generally reflect this decline in usage with the majority of RHAs significantly changing. Several rural RHAs (Burntwood, Churchill, & Parkland) had increases in meperidine usage; but, these changes were not statistically significant. Of these, both Burntwood and Churchill were already low, with rates of use less than half of the provincial average. The high relative increase in Churchill is related to an exceeding low initial rate of use and the very small population (under 800 persons) serviced in this region.

Three rural RHAs (Parkland, Nor-Man, and South Eastman) had rates of use well above the average throughout the study, with the rate in Parkland having increased to twice the provincial average. This region reported the highest amount of use in the province. The two other above average regions did demonstrate a decline in use, with South Eastman region dropping to a third of its peak use within the study period.

This type of regional analysis suggests that broad based provincial educational efforts may be unnecessary. Targeted educational efforts in a small number of regions may be a better use of resources. Manitoba rates of meperidine use appear to be among the lowest in the country. The MB provincial average reported here of 7.9 DDD/1000 population per quarter compares favourably with estimated rates of 9 to 81 DDD/1000 population per quarter for other provinces.[15]

The prescriber data also showed a 50% decline in the number of physicians' prescribing meperidine over this ten year period. By the end of the study only 4% of physicians had written a prescription for meperidine during any three month period. Since 96% of physicians had not written a single prescription for meperidine in a particular quarter, it would appear that there is widespread understanding of the limitations of this drug. Similar to targeted regional education efforts, perhaps educational efforts targeted at specific prescribers would be more helpful. An educational effort in Nova Scotia involved sending targeted letters to the small number of physician's prescribing meperidine in their province. This inexpensive intervention produced a 12% decline in patients using meperidine.[16]

The pattern of decline in provincial DDD rates began shortly after the publication of the second ISMP bulletin in the summer of 2005. It would appear that either directly or indirectly (e.g. changes in hospital policies), prescribing could have been influenced by these safety bulletins.

While our results are encouraging, the potentially inappropriate use of meperidine has not been eliminated. It has been suggested that removing meperidine from the provincial formulary, or severely restricting its use, may be a reasonable next step in limiting its use. This action has been taken in some provinces (Nova Scotia and Northwest Territories have removed meperidine from their formulary, and Ontario has restricted it to a maximum duration of 1 week of use). This idea is not without its' detractors, and several specific reasons to continue listing meperidine have been given. One objection to formulary removal is the belief that meperidine is especially effective in pancreatitis and biliary spasm. A number of studies have looked at this issue by directly comparing morphine to meperidine for this indication. No increased benefit has been seen with the use of meperidine, and some studies have shown it to be inferior.[3,4,8] Similar results are seen in the treatment of other types of pain.[8,9]

The most common reason given to keep meperidine listed is for use in patients allergic to other opioids. While allergies to opiates are frequently reported, true opiate allergy is actually rare with the majority of reported allergy symptoms actually being typical opioid side effects such as nausea, vomiting, and pruritus. Many of these side effects are self-limiting, decrease with continued use, and have been shown to be just as, or even more, common with the use of meperidine.[17] Even in patients with a true allergy to the natural and semi-synthetic opiates, use of oral meperidine remains a poor choice due to its short duration (2-3 hrs.) and toxicity. Instead, patients with true opiate allergy should be managed with either a non-opioid analgesic such as an NSAID, or, for severe pain, a structurally dissimilar opioid such as fentanyl.

Meperidine is still the drug of choice for a few specific indications: the prevention or treatment of blood transfusion induced rigors, post-operative shivering, and some chemotherapy-related reactions. Removal of meperidine from the community formulary would not affect this use, and many hospitals already restrict meperidine use to these indications.

Our cross-sectional review of meperidine use in Manitoba suggests that there has been a substantial decline in usage over the past 10 years. There has been a simultaneous increase in overall opioid prescribing, with the number of DDDs/1000 persons rising 35% from 2005 to 2010.[15] This decline is temporally associated with the release of the second ISMP bulletin issued in April of 2005, suggesting a possible beneficial effect of such warning. While meperidine use was in decline prior, the rate of decrease increased substantially immediately following the publication of these warnings.

With 96% of physicians no longer actively prescribing this medication, we may have reached the limits of general educational measures. Our regional review suggests that any further educational efforts should be focused on regions with high rates of use, or on the small number of physicians' potentially prescribing meperidine outside of recommended guidelines. Alternatively, the time may have come to use policy levers and a disincentive to continued use of meperidine. Given the small number of appropriate uses, delisting coverage and requiring special permission for the rare number of appropriate uses, would seem a logical next step in enhancing patient's safety.

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