The effect of an educational intervention on meperidine use in Nova Scotia, Canada: a time series analysis

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Abstract

Purpose—To evaluate the impact of a prescriber focused individual educational and audit–feedback intervention undertaken by the Nova Scotia Prescription Monitoring Program (NSPMP) in March/April 2007 to reduce meperidine use.

Method—The NSPMP records all prescriptions for controlled substances dispensed in community pharmacies in Nova Scotia, Canada. Oral meperidine use from 1 July 2005 to 31 December 2009 was examined using NSPMP data. Monthly totals for the following were obtained: number of individual patients who filled at least one meperidine prescription, number of prescriptions, and number of tablets dispensed. Data were analyzed graphically to observe overall trends. The intervention effect was estimated on the logarithmic scale with autocorrelations over time modeled by an integrated autoregressive moving average model for each outcome measure.

Results—An overall trend toward decreasing use from July 2005 to December 2009 was apparent for all three outcome measures. The intervention was associated with a statistically significant reduction in meperidine use, after adjusting for the overall long-term trend. Compared with the pre-intervention period, the monthly number of patients declined by 12% ($p < 0.001$; 95%

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CONFLICT OF INTEREST

Judith Ellen Fisher and Ingrid Sketris have received unrestricted research grants from the Nova Scotia Department of Health and Wellness, which funds the NSPMP. Ingrid Sketris has also received compensation from Green Shield Canada and Health Canada and holds a Canadian Health Services Research Foundation and Canadian Institutes of Health Research Chair in Health Services Research, cosponsored by the Nova Scotia Health Research Foundation.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Supplementary Figure 1: Monthly number of patients pre-intervention: July 2005 to March 2007; and post-intervention: April 2007 to December 2009, on the logarithmic scale. Dotted line is a LOWESS smoothing line. Solid vertical line is the time of the educational intervention.

Supplementary Figure 2: Monthly number of prescriptions pre-intervention: July 2005 to March 2007; and post-intervention: April 2007 to December 2009, on the logarithmic scale. Dotted line is a LOWESS smoothing line. Solid vertical line is the time of the educational intervention.

Supplementary Figure 3: Monthly number of tablets pre-intervention: July 2005 to March 2007; and post-intervention: April 2007 to December 2009, on the logarithmic scale. Dotted line is a LOWESS smoothing line. Solid vertical line is the time of the educational intervention.

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confidence interval [CI] = 5%–18%), prescriptions by 10% ($p < 0.001$; 95%CI = 3%–17%), and tablets by 13.5% ($p < 0.001$, 95%CI = 6%–29%) in the post-intervention period.

Conclusion—Given the risks associated with meperidine, determining that this intervention successfully reduced meperidine use is encouraging. This study highlights the potential for using population data such as the NSPMP to evaluate the effectiveness of population-level interventions to improve medication use, including professional, organizational, financial, and regulatory initiatives.

Keywords

educational intervention; meperidine; pethidine; time series analysis

INTRODUCTION

Meperidine (Demerol®) is a synthetic opioid analgesic that has been prescribed extensively since its introduction more than five decades ago. However, numerous reviews have failed to demonstrate a clear therapeutic advantage of meperidine compared with other opioids. A short duration of action and the accumulation on repeated doses of the active metabolite normeperidine limit its use in the management of chronic pain. Normeperidine is a weak analgesic but a potent central nervous system (CNS) irritant that can precipitate adverse effects ranging from agitation to tonic-clonic seizures.^{1,2} Meperidine use presents additional patient safety concerns compared with other analgesics.³ For example, non-opioid neurotoxicity that is not responsive to naloxone renders meperidine overdose particularly dangerous.³

Recognition of the adverse consequences associated with meperidine use and its overall unfavorable risk–benefit profile in all patient populations has resulted in a progressive movement away from meperidine use. American guidelines issued by the Joint Commission on Accreditation of Health Care Organizations, the Agency for Health Care Policy and Research (AHCPR), and the American Pain Society (APS) discourage meperidine use.^{4–7} Golembiewski (2002) reported that the AHCPR recommends “that oral meperidine should not be used for pain management”⁸ (p. 123) and “that parenteral meperidine should be restricted to patients who have a true allergy or intolerance to other opioids”⁸ (p. 124). Further, the APS recommends that meperidine should not be used for more than 48 hours for acute pain, and then only in patients with normal renal function and without any pre-existing CNS conditions.^{6,9} Meperidine use is viewed as an indicator of poor quality care for many government, professional, and accreditation agencies.² The Institute for Safe Medication Practices Canada issued a bulletin in August 2004 recommending that Canadian health care facilities evaluate their use of meperidine and consider adopting the American recommendations.¹⁰ Many public sector Canadian drug plans do not list meperidine as a reimbursable treatment. For example, Veterans Affairs Canada authorizes meperidine in special cases only and never for chronic pain management.¹¹ Oral meperidine has not been a reimbursable treatment under the Nova Scotia Pharmacare Program (NSPP) since 1998.

Interventions including educational initiatives supported by formulary restrictions and assessment of prescribing patterns have successfully reduced and even eliminated

meperidine use in some jurisdictions and institutions.^{12–15} Nevertheless, meperidine use continues, in particular, in surgical patients.^{2,16} Furthermore, data from the American public health surveillance system, the Drug Abuse Warning Network (DAWN), suggest that the misuse of meperidine remains problematic. DAWN estimated that non-medical use of meperidine was associated with almost 1500 emergency room visits in 2006.^{17,18} This number was substantially lower than those associated with other opioid analgesics, such as oxycodone combination products, but represented an increase over the previous 2 years.¹⁷

In Canada, meperidine is designated by federal¹⁹ and provincial legislation as a “controlled substance”; therefore, its prescription, dispensing, and consumption are regulated and monitored. In the province of Nova Scotia, monitoring of prescribed controlled substances dispensed in the community (i.e., does not include hospital-provided medications) is the responsibility of the Nova Scotia Prescription Monitoring Program (NSPMP).²⁰ The objective of this research was to evaluate an NSPMP intervention to decrease meperidine prescribing. It was hypothesized that the intervention would be associated with a significant decline in meperidine use.

METHODS

The intervention

The legislated mandate of the NSPMP is to promote the appropriate use of monitored drugs and the reduction of their abuse and misuse.²⁰ The NSPMP reviews and investigates patterns of use that suggest potentially inappropriate use such as multiple prescriptions from multiple prescribers that are filled at multiple pharmacies over a 30-day period for one individual or that exceed specific dose or quantity thresholds. In response to concern regarding the continued use of meperidine in Nova Scotia, the NSPMP undertook an intervention in March and April 2007 for selected meperidine prescribers¹ in Nova Scotia. The prescribers selected were the highest 30 prescribers of meperidine over the previous 1-year period, that is, April 2006 through March 2007. These 30 practitioners represent only 2.4% of all practitioners who prescribed at least one prescription for meperidine tablets that was filled in a community pharmacy during this time but accounted for about 25% of all meperidine prescriptions and 40% of tablets dispensed.²¹

The intervention included the provision of an educational component consisting of three scholarly articles addressing the potential risks and benefits associated with meperidine^{9,10,22} and individualized audit and feedback letters that detailed that prescriber's meperidine prescribing patterns. The letters were printed on stationary with the NSPMP letterhead, and the packages were prepared by NSPMP staff and mailed to the prescribers from the NSPMP.

The total direct cost of the intervention to the NSPMP was \$208.42 and included the costs of the preparation and mailing of the packages by NSPMP staff, stationary, and postage.²³ The Drug Evaluation Unit of the Capital District Health Authority Pharmacy Department in

¹In Nova Scotia, prescribing authority for controlled substances, including opioids, is restricted to physicians and dentists. None of the prescribers for this intervention was a dentist.

Halifax Nova Scotia also provided in-kind support regarding the critical analysis of the literature and article selection; these indirect costs are not included in the cost estimate.

Study population

Nova Scotia is a Canadian province with a population of approximately 940 000.²⁴ Nova Scotians receive care from approximately 1100 active family physicians and 1100 medical specialists.²⁵ Data were extracted from the NSPMP database for all Nova Scotia residents who filled at least one prescription for oral meperidine tablets from 1 July 2005 to 31 December 2009.

Data source and data extraction

The NSPMP maintains an electronic database that contains patient, prescriber, and drug-related information on all monitored prescription drugs dispensed in Nova Scotia.^{20,26} Approval was received from the Research Ethics Board, Dalhousie University, Halifax Nova Scotia for the NSPMP to release data to the authors for analysis (Project 2012–2149, 10 May 2010). The NSPMP limited the release to aggregated patient and prescription data to ensure the confidentiality of individual patients and prescribers.

The NSPMP provided the authors with aggregated data on the number of individuals who filled a prescription for meperidine tablets,² number of oral meperidine prescriptions filled, and number of meperidine tablets dispensed by month from July 2005 to December 2009. The focus of this study was oral (50 mg) tablets because the NSPMP monitors prescriptions dispensed in community pharmacies. These pharmacies meet the needs of persons living in their own homes as well as in long-term care facilities.

Data analysis

The data were examined graphically to observe the overall trends and to identify seasonal patterns and potential outliers. Some peaks were observed in the number of prescriptions in January and March during the years 2006 and 2007 and in the number of tablets in March 2006 and 2007; however, these seasonal patterns were not consistent over time. There was no consistent seasonal pattern evident for the number of patients. The second data point for the number of tablets (August 2005) was identified as a potential outlier; therefore, the first two data points for tablets were deleted.

Each measure (i.e., number of patients, prescriptions, and tablets) was visualized by paired scatter plots with fitted smoothing lines against time (i.e., each month) before and after the intervention. The smoothing line was obtained using robust locally weighted regression (LOWESS) to explore any change in the mean level before and after intervention.²⁷

The intervention model²⁸ was fitted by a two-stage modeling approach to determine whether the observed trend was due to the long-term trend, the intervention, or both. The model was initially assumed to be independent and normally distributed. After fitting the best general linear model (GLM), plots of the residual autocorrelation function were examined to check

²Meperidine oral tablets are available in Canada as 50 mg tablets.

the possible autocorrelation for dependence. If autocorrelation was detected, a suitable model was determined for the residual process as the initial time series model, and the final model was refitted using time series model selection and estimation procedures.²⁹

To detect the impact of the intervention, we considered the intervention effect as the main factor, controlling for the effect of the long-term linear trend as a covariate, and constructed the best GLM for each outcome measure, that is, patients, prescriptions, and tablets, on a log scale. The log scale stabilizes the data variation and transforms the data into a normal distribution. The residual diagnostic checks for the model indicated that the logarithmic transformation was appropriate. The R^2 value from the least square estimation was examined to determine whether a linear additive model for the data was reasonable. The R^2 value from each of the fitted GLM models was reasonably high (0.91 for patients, 0.88 for prescriptions, and 0.89 for tablets), suggesting that on a log scale, a linear additive model of a long-term trend and intervention factor was reasonable. However, residual autocorrelation plots indicated some serial dependence in all three outcome measures, so a time series regression analysis should be considered. Therefore, a time series regression model, formulated for a stepwise intervention, was fitted for each outcome measure. More specifically, the intervention effect was analyzed on a log scale, with the autocorrelations and the long-term trend over time adjusted by an integrated autoregressive moving average model (ARIMA). The ARIMA model includes an integrated component that controls for the long-term trend over the entire study period and therefore accounts for the potential confounding effect of the overall trend. The final model was selected based on the automatic Akaike information criterion. The adequacy of the three final models was examined using the following residual diagnostic checks: the residual normal probability plot and the Shapiro–Wilk test for testing normality and the standardized residual plots, autocorrelation plots of the residuals, and the Ljung–Box test for checking the independence. The results from these diagnostic checks indicated that the final models provided adequate fits and satisfied the distribution assumptions overall. Data analyses were conducted using R.2.10.1 (available from the Comprehensive R Archive Network at www.r-project.org)

RESULTS

Table 1 presents descriptive statistics for each outcome measure. Fewer patients filled prescriptions for meperidine in the post-intervention period (April 2007 to December 2009), compared with the pre-intervention period (July 2005 to March 2007). Similarly, on average, fewer prescriptions were filled and fewer tablets were dispensed after the intervention.

Figures 1, 2, and 3 show the smoothing scatter plot of the pre-intervention and post-intervention number of patients, prescriptions, and tablets. A downward trend over the two study periods is apparent for all three measures, with a stepwise decrease in the post-intervention period. The slopes of the trends over the two periods look similar.

Because there was no significant change in the slope of the trend, the simple stepwise intervention effect was estimated using time series regression. The autocorrelation and the long-term trend over time were adjusted by ARIMA (2, 1, 1), ARIMA (2, 1, 0), and ARIMA (2, 1, 0) for patients, prescriptions, and tablets, respectively. Table 2 presents a summary of

the results of the final fitted model for each of the outcome variables on a log scale. The estimated changes in percentage for each outcome measure are as follows: $100 * (\exp(-0.1291) - 1) = -12.11$ ($p < 0.001$, one-sided³) for the number of patients; $100 * (\exp(-0.1066) - 1) = -10.11$ ($p = 0.003$, one-sided) for the number of prescriptions; and $100 * (\exp(-0.1451) - 1) = -13.51$ ($p < 0.001$, one-sided) for the number of tablets. The residual diagnostic checks for the three final models indicated that they were adequate to describe the data.

DISCUSSION

Meperidine use decreased from July 2005 to December 2009 according to all three outcome measures. Beyond the general downward trend in meperidine use over time, the time series analysis revealed a statistically significant reduction in meperidine use at the time of the intervention. Compared with the pre-intervention period, in the post-intervention period, the monthly numbers of patients redeeming meperidine prescriptions declined by 12%, prescriptions by 10%, and meperidine tablets dispensed by 13.5%.

The apparent success of the intervention is encouraging given that the evidence regarding the effectiveness of educational interventions on changing practitioner behavior is mixed^{30–35} and that the effect size for such interventions is modest. For example, a systematic review of 18 studies addressing the effectiveness of the dissemination of educational materials on guideline implementation found overall modest (median effect = 8.1%, range = 3.6%–17.0%) but short-term improvements.^{32,33} Audit and feedback interventions have also been demonstrated to change practitioner behavior (median effect = 7%, range = 1.3%–16.0%),^{31,32,34,36} although the effect of the intervention is dependent on the context.³⁵ Therefore, the effect size for the NSPMP meperidine intervention, 10%, 12%, and 13.5%, respectively, for the three outcome measures, is noteworthy, especially given the low cost of the intervention and that the overall downward trend was sustained for 33 months.

The fact that the materials were sent by the NSPMP, on their letterhead, might have enhanced the intervention's impact. Although representatives from the Nova Scotia Colleges of Physicians and Surgeons, Dentists and Pharmacists serve on the governing board of the NSPMP,^{20,26} the program is administered at arm's length from the professional licensing and regulatory bodies and therefore does not have direct authority regarding licensure. However, the NSPMP does have a legislated mandate to review claims for all monitored drugs on a regular basis and has the authority to request clarification from practitioners regarding any potentially inappropriate patterns that become evident. If questions remain, the case will be reviewed by the Drug Utilization Review Committee and may also be referred to the NSPMP Practice Review Committee (PRC). The PRC is a peer-review committee comprised of physicians, dentists, and pharmacists. The committee may either terminate the investigation and close the case or take further action, including referral to the NSPMP's medical consultant, the appropriate licensing authority, or the appropriate law enforcement authority.²⁰ Thus, practitioners may interpret any correspondence from the

³The research hypothesis was that the intervention would be associated with decreased use; therefore, the one-sided (i.e., ordered alternative) test was used.

program as potentially having serious consequences, increasing the perceived importance of the intervention materials.

The trend toward decreased meperidine use may be due to increasing awareness by prescribers of meperidine's risks and is consistent with other jurisdictions.¹ From 2005 to 2009, the adult (19+ years) population of Nova Scotia increased slightly (2.7%), from about 748 000 to about 768 000²⁴; therefore, the decline in meperidine use is not the result of an overall population decrease. Opioid analgesic choices available to prescribers did not change appreciably during the study period; with the exception of the buprenorphine/naloxone combination that is used to treat opioid dependency, rather than pain management, no new chemical entities became available on the Canadian market during the study period.³⁷ Therefore, the availability of new products does not appear to be a factor either. No other government-sponsored interventions or continuing professional (medicine or pharmacy) education programs or Nova Scotia Pharmacare policy changes regarding opioids occurred at the time of this intervention that would have impacted meperidine use. Furthermore, the cost of meperidine tablets (about 12 cents/tablet)³⁸ remained stable over the study period.

Despite the general decrease in meperidine use in recent years, oral meperidine continues to be prescribed and dispensed in Nova Scotia. On average, 850 prescriptions for 70 000 meperidine tablets were dispensed per month in the post-intervention period. Based on the 2009 data from the Canadian Institute for Health Information, approximately 39% of all prescriptions in Nova Scotia are publicly funded³⁹ and therefore subject to the benefit criteria of these programs, including the NSPP.⁴⁰ Oral meperidine has not been a reimbursable treatment under the NSPP since 1998; patients who fill prescriptions for meperidine are either paying out of their own pockets or have private sector coverage that continues to list meperidine as a benefit. Therefore, future educational programs and other interventions designed to promote disinvestment^{41–43} in meperidine and to facilitate switching to a more appropriate analgesic must be directed toward both public and private sector payers and toward patients, either directly or through health care professionals. In addition, further work is needed to determine if broadening the intervention strategy to more prescribers, for example, those in the top quartile, would have a further benefit. It would also be useful to determine for which prescribers such interventions work best, why, and under what circumstances.⁴⁴

There were limitations in the analyses reported herein. First, the number of available data points was limited to 54 because of the timeframe of the intervention. Although a larger sample size would be desirable, the Box and Tao approach used in these analyses has been demonstrated to be accurate for even moderately small samples.⁴⁵ For privacy and confidentiality reasons, individual-level data were not made available by the NSPMP. Therefore, it was not possible to track the patterns for specific patients and prescribers. In particular, the patients and prescriptions of the 30 physicians who received the educational and individualized audit intervention could not be tracked separately from all other meperidine prescriptions and patients in the province. Furthermore, information was not available regarding patient diagnoses, drug use history, drug insurance status, possible contraindications or other issues related to the choice of meperidine for a specific patient, or other contextual issues that might impact prescribing patterns, for example, information

sessions sponsored by organizations not affiliated with academia. In addition, changes in the private insurers' coverage of meperidine over the study period could not be determined. Finally, data on prescriptions filled in hospital are not captured by the NSPMP.

CONCLUSIONS

An educational intervention with an individualized audit report that was mailed to the 30 prescribers with the highest rates of meperidine use was associated with a reduction in the use of meperidine overall in the province. This intervention was carried out because meperidine has a poor risk–benefit profile. Nevertheless, the continued use of this medication warrants concern and further investigation of the patient, provider, and health system factors that hinder or facilitate disinvestment with meperidine and the uptake of more appropriate opioid analgesics.

Acknowledgments

The authors acknowledge the Drug Evaluation Alliance of Nova Scotia, Nova Scotia Department of Health and Wellness. The following are the postdoctoral funding sources for Judith Fisher: Network for End of Life Studies Interdisciplinary Capacity Enhancement, funded by Canadian Institutes for Health Research (CIHR) through a strategic initiative grant (HOA-80067), 2006–2011, and The Drug Use Management and Policy Residency, a summer studentship, funded by the Canadian Health Services Research Foundation (CHSRF), CIHR, and the Nova Scotia Health Research Foundation (NSHRF). Ingrid Sketris holds a CHSRF/CIHR Chair in Health Services Research, cosponsored by the NSHRF. The funders had no role in the collection, analysis, and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

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KEY POINTS

- An educational intervention, with an individualized audit report that was mailed to the 30 prescribers with the highest rates of meperidine use, was associated with a reduction in the overall use of meperidine in the Canadian province of Nova Scotia.
- The continued use of meperidine in Nova Scotia warrants concern and further investigation of the patient, provider, and health system factors that hinder or facilitate disinvestment with meperidine and the uptake of more appropriate opioid analgesics.

Figure 1. Monthly number of patients before intervention (July 2005–March 2007) and after intervention (April 2007–December 2009). The dotted line is the LOWESS smoothing line. The solid vertical line is the time of the educational intervention

Figure 2. Monthly number of prescriptions before intervention (July 2005–March 2007) and after intervention (April 2007–December 2009). The dotted line is the LOWESS smoothing line. The solid vertical line is the time of the educational intervention

Figure 3. Monthly number of tablets before intervention (July 2005–March 2007) and after intervention (April 2007–December 2009). The dotted line is the LOWESS smoothing line. The solid vertical line is the time of the educational intervention

Table 1

Monthly number of patients receiving meperidine, meperidine prescriptions, and meperidine tablets dispensed before and after an educational intervention in Nova Scotia, Canada (July 2005 to December 2009)

	Number of patients		Number of prescriptions		Number of tablets dispensed	
	Pre-intervention (July 2005–March 2007)	Post-intervention (April 2007–December 2009)	Pre-intervention (July 2005–March 2007)	Post-intervention (April 2007–December 2009)	Pre-intervention (July 2005–March 2007)	Post-intervention (April 2007–December 2009)
Number of time points (months)	21	33	21	33	19	33
Mean (SD)	943.2 (52.1)	713.6 (72.3)	1103.5 (60.5)	853.8 (83.0)	94 295.4 (6527.4)	69 929.3 (6037.7)
Median	946	701	1116	831	94 112	70 084

Table 2

Summary of the estimated intervention effect from fitting the time series regression model to the data for each outcome measure on a log scale based on data from the Nova Scotia Prescription Monitoring Program, July 2005 to December 2009

	Estimate	Standard error	95% Confidence interval of estimate	Estimated percentage change [*]
Number of patients	-0.1291	0.0376	(-0.203, -0.055)	-12%
Number of prescriptions	-0.1066	0.0395	(-0.184, -0.029)	-10%
Number of tablets	-0.1451	0.0401	(-0.224, -0.067)	-13.5%

^{*} Calculated for each outcome measure according to the formula: $100 * (\exp(\text{estimate}) - 1)$.