

Adherence to Guidelines and the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions Criteria for Colchicine Dosing for Gout Treatment in Beneficiaries of the Nova Scotia Seniors' Pharmacare Program

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ABSTRACT

Purpose: Colchicine is commonly used in the management of gout; however, older persons have higher risks of toxicity. Accordingly, the Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP) criteria for colchicine consider >3 months of treatment as potentially inappropriate in older persons. Recent evidence also suggests lower dosing of colchicine is as effective and results in fewer toxicities than high-dose colchicine. The objectives of this study were to determine the dose, duration, and prescribers of colchicine and to evaluate adherence to the STOPP criteria and international guidelines for colchicine in older persons.

Methods: A retrospective, observational study was conducted from April 1, 2006 to March 31, 2011 to evaluate colchicine use. Nova Scotia Seniors' Pharmacare Program beneficiaries who met inclusion criteria for an incident case of gout and who filled at least 1 prescription for colchicine during the study period were included. Colchicine dose and duration were reported descriptively. Multivariate logistic regression was used to identify predictors of the study population in making a claim for colchicine >90 and >180 days.

Findings: A total of 518 persons were dispensed 1327 courses of colchicine during the study period. The mean daily dose of colchicine ranged from 1.39 to 1.50 mg. Colchicine doses >1.2 mg were prescribed in approximately one-third of the study population.

Colchicine was prescribed for >90 days in 14.2% of treatment courses and for >180 days in 8.1% of treatment courses. Female sex was the only predictor of treatment duration >90 days.

Implications: This study is the first to report on colchicine dose and duration using STOPP criteria in a specific cohort of older persons with incident gout. Strategies to improve colchicine prescribing in older persons are needed. (*Clin Ther.* 2015;■:■■■-■■■) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: colchicine, dose, duration, gout, older persons.

INTRODUCTION

Gout is common, with ~2.7% of men and women aged >19 years in the United States reporting a diagnosis. Gout affects older persons more frequently. The estimated lifetime prevalence of gout is lowest (0.4%) in those aged 20 to 29 years and highest (7.3%) in those aged 70 to 79 years.¹

Colchicine is recommended as a first-line alternative to nonsteroidal anti-inflammatory drugs in the management of acute gout attacks and as prophylaxis in combination with urate-lowering therapies (ULTs) such as allopurinol.^{2,3} It substantially improves pain and inflammation associated with acute attacks

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compared with placebo.^{4,5} Colchicine was historically dosed as 1 mg, followed by 0.5 mg every 2 hours until complete response or toxicity.⁶ Nausea, vomiting, and other adverse effects associated with this regimen were reported,^{4,6} leading investigators to conclude that lower dosing of colchicine may be warranted.⁶

Evidence from 2010 suggests that low-dose colchicine (1.8 mg over 1 hour) has similar efficacy and less toxicity than high-dose colchicine (4.8 mg over 6 hours) in management of acute gout.⁵ Guidelines from the American College of Rheumatology (ACR) published in 2012 and the European League Against Rheumatism (EULAR) published in 2006 recommend low-dose colchicine (1.8 mg over 1 hour, followed 12 hours later with 0.6 mg once or twice daily and 0.5 mg three times daily, respectively) for acute gout attacks.^{2,3,7} When used in combination with allopurinol for 3 to 6 months,⁸ colchicine prevents acute attacks of gout.^{3,8-12} The 2012 ACR guidelines provide the strongest recommendation (evidence A) for continuation of colchicine for 6 months after initiation of ULT³ with ULT continued as monotherapy indefinitely.⁷

Older persons have higher risks of toxicity with colchicine due to increasing rates of renal or hepatic dysfunction.¹³ Older persons are also at increased risk of serious adverse effects, including neuromuscular toxicity and rhabdomyolysis.¹⁴ Polypharmacy may also limit use of colchicine.¹³ Colchicine is a cytochrome P450 3A4 and P-glycoprotein substrate. Life-threatening and fatal interactions were reported when used in combination with P-glycoprotein and strong cytochrome P450 3A4 inhibitors.¹⁴

To minimize toxicity, the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria were developed and validated with the use of a Delphi consensus technique to provide prescribers with a screening tool that consisted of 65 evidence-based criteria for appraising older patients' medications.¹⁵ The STOPP criteria have provided guidelines for colchicine usage in the management of gout.¹⁵ The initial version of the STOPP criteria, published in 2008, indicated long-term use of colchicine as a criterion for potentially inappropriate prescribing but did not specify duration.¹⁵ Although not available during the study period, revised STOPP guidelines indicate potentially inappropriate prescribing of colchicine for durations > 3 months.¹⁶

The study objectives were to determine the dose and duration of colchicine and to evaluate adherence

to the STOPP criteria and international guidelines for colchicine dispensed for Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries.

METHODS

This study examined trends in colchicine prescriptions for NSSPP beneficiaries dispensed in Nova Scotia from April 1, 2006 to March 31, 2011. The study was approved by the Dalhousie University Research Ethics Board reference number 2012-2657.

Study Population

The study population included all beneficiaries of the NSSPP who met inclusion criteria for an incident case of gout and who filled at least 1 prescription for colchicine during the study period. Eligibility for the NSSPP includes age ≥ 65 years, permanent residency status in Nova Scotia, and a valid health card with no other current prescription drug coverage through a private insurance provider.¹⁷ In 2010, NSSPP provided benefits to $\sim 68\%$ of the population aged ≥ 65 years in Nova Scotia. In 2013 and 2014, approximately 7.5% of NSSPP beneficiaries who lived in long-term care homes were included in this study (personal correspondence, Mike Joyce, MBA, Director Health Economics, Government of Nova Scotia).

Study Design and Data Collection

A retrospective observational methodology was used. Data of NSSPP beneficiaries was accessed by Health Data Nova Scotia in the Department of Community Health and Epidemiology at Dalhousie University. Potential incident cases of gout over the period of April 1, 2006 to March 31, 2011 were identified by excluding any individuals with a diagnosis of gout in the previous 5 years. Incident cases also had to have at least 2 physician diagnosis for gout in the physician visit administrative claims data (ICD9 274.xx or ICD10 M10.xx) at least 30 days apart within a 12-month period. Other researchers have used this algorithm to capture incident cases of gout.^{18,19} A total of 2558 NSSPP beneficiaries were identified with incident gout during the study period.

Colchicine was identified with the use of the Drug Identification Number and the World Health Organization, Anatomical Therapeutic Chemical classification 2014 M04AC01.²⁰ For all colchicine users in our cohort, we determined demographic characteristics of

beneficiaries, number of individuals prescribed colchicine, the dose and duration of colchicine prescriptions, and the type of physician (general practitioner vs specialist) who diagnosed gout. For each identified beneficiary who received colchicine, we grouped individual prescriptions into treatment courses on the basis of the start and end dates of each prescription. The end date of the initial prescription was calculated as the date the prescription was dispensed plus the days supplied. If the gap between the end of the initial prescription and the start of the next prescription was ≤ 14 days, it was considered to be part of the same treatment course as the previous prescription. If this gap was > 14 days, this prescription was taken to represent the start of a new treatment course. Sensitivity analysis was performed with a 30-day treatment gap and resulted in similar patterns (data not shown). The prescribed daily dose for each treatment course was calculated as the total dose dispensed (quantity of drug dispensed \times strength of drug) divided by the total days dispensed over a given treatment course. The aggregate days of treatment within each course were categorized into the following specific time periods: (1) ≤ 3 days, (2) 4 to 7 days, (3) 8 to 14 days, (4) 15 to 30 days, (5) 31 to 60 days, (6) 61 to 90 days, (7) 91 to 180 days, and (8) > 180 days.

Kaplan-Meier survival curves were generated to illustrate the proportion of beneficiaries by the duration of their treatment course for all patients having a treatment course > 7 days ($n = 417$). Separate survival curves were generated according to the calendar year in which the treatment course began. A single beneficiary could be represented by ≥ 1 treatment courses contained within a single year, spanning ≥ 1 years, or multiple courses within/across multiple years.

Data were analyzed to determine the number of patients who received ≤ 1.2 mg/d, ≤ 1.5 mg/d, and > 1.5 mg/d by calendar year (April 1, 2006 to March 31, 2011) to assess adherence to dosing recommendations by the ACR and EULAR guidelines for management of acute gout (beyond the first day of treatment) and chronic gout.^{4,7} Concordance for prescribing of colchicine for prevention of acute attacks during initiation of ULT with STOPP criteria version 1 and the ACR guidelines was determined by evaluating the number of patients who received a total duration of ≤ 90 days, ≤ 180 days, and > 180 days.

Statistical Analysis

Descriptive statistics were used to summarize NSSPP beneficiaries by age categories and sex. The proportion of beneficiaries who received at least 1 prescription for colchicine in a fiscal year from April 1, 2006 to March 31, 2011 was divided into the following subpopulations: (1) patient aged 65 to 69, 70 to 74, 75 to 79, 80 to 84, and ≥ 85 years; (2) patient sex; and (3) prescriber specialty (general practitioner vs specialist). For each group, we measured dose intensity, measured by prescribed daily dose, and duration of colchicine use as measured with the use of prescription start and stop dates divided into the following categories: (1) ≤ 3 days, (2) 4 to 7 days, (3) 8 to 14 days, (4) 15 to 30 days, (5) 31 to 60 days, (6) 61 to 90 days, (7) 91 to 180 days, and (8) > 181 days.

Multivariate logistic regression was performed to identify predictors of NSSPP beneficiaries aged ≥ 65 years making a claim for colchicine > 90 and > 180 days. Potential predictors included the year colchicine was initially prescribed, patient sex and age. All analyses were performed with SAS/STAT software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

From April 1, 2006 to March 31, 2011, 903 unique NSSPP beneficiaries met criteria for incident gout and were dispensed drug therapy for management of gout as defined by our methods. Of these beneficiaries, 518 individuals were dispensed a total of 1327 courses of colchicine between April 1, 2006 and March 31, 2011. Baseline characteristics are summarized in [Table I](#). The majority (55.0%) in our study cohort were aged ≥ 75 years at the date of their first prescription for colchicine and slightly more than one-half (50.2%) were women. Most patients (92.5%) in our cohort were coded with a diagnosis of gout by their general practitioner.

The mean (SD) prescribed daily dose of colchicine received by NSSPP beneficiaries (including day 1 of therapy) ranged from 1.39 (1.08) mg to 1.50 (1.02) mg during the study period. Despite lower dosing recommendations from EULAR and ACR, colchicine doses > 1.2 mg were prescribed in approximately one-third of the study population in each fiscal year. The proportion of treatment courses ≤ 1.2 , ≤ 1.5 , and > 1.5 mg/d by fiscal year is outlined in [Table II](#). The logistic model suggested that women were significantly less likely than men to be prescribed colchicine for > 90 continuous days, but age and the

Clinical Therapeutics

Table I. Baseline characteristics of Nova Scotia Seniors' Pharmacare Program beneficiaries receiving colchicine therapy.

Characteristic	N	%
Male	258	49.8
Female	260	50.2
Age, y*		
65-69	120	23.2
70-74	113	21.8
75-79	116	22.4
80-84	90	17.4
≥85	79	15.3

*Age at date of first prescription for colchicine.

year of the prescription were not significant. None of these factors were significant in predicting >180 days of continuous prescribing. Overall, the 90- and 180-day models correctly predicted 60% and 62% of observed durations, respectively.

The majority (75.4%) of treatment courses were prescribed for >7 days. The duration of colchicine use by year on the basis of 14-day treatment gaps for ≤90 days, ≤180 days, >180 days, and cumulative days of colchicine use by fiscal year are outlined in Figures 1 and 2. Colchicine was prescribed for ≤90 days in 85.8% of treatment courses and for ≤180 days in 91.9% of treatment courses. A total of 8.1% of courses were continued for >6 months. The proportion of beneficiaries who received colchicine >90 days remained consistent from 2006 to 2010 (14.1% vs 14.9%) despite

publication of initial recommendations from STOPP criteria in 2008 which suggested prolonged use of colchicine as potentially inappropriate. The proportion of beneficiaries exceeding >180 days also remained consistent from 2006 to the end of 2010 (8.1% vs 9.8%). Women were significantly less likely than men to have a duration >90 days, but, as shown in Table III, no other factors were significant predictors of having a treatment duration >90 or 180 days.

DISCUSSION

The mean prescribed daily dose (ranging from 1.39 to 1.50 mg from 2006 to 2011) exceeded current dosing recommendations of 0.6 mg once or twice daily for management of acute gout (after the initial dosing of 1.8 mg in the first hour) and chronic gout.⁴ In addition, a potentially concerning 27.9% to 38.7% of study participants received >1.2 mg/d between April 1, 2006 and March 31, 2011. NSSPP beneficiary treatment courses (14.2%) exceeded durations of >3 months and 8.1% of beneficiary treatment courses continued >6 months of prophylaxis despite the recommendation by STOPP version 1 to avoid prolonged use of colchicine. Despite publication of EULAR guidelines in 2006, STOPP criteria in 2008, and the landmark trial by Terkeltaub in 2010, no significant change in colchicine dosing or duration was observed over the course of the study. Women were significantly less likely to receive longer durations of colchicine than men, suggesting men are at greater risk of inappropriate duration of colchicine use. However, the moderate fit of the logistic models suggested that other unobserved factors also had a substantive impact on prescribing decisions.

Table II. Colchicine dosing by calendar year (April 1, 2006 to March 31, 2011) in Nova Scotia Seniors' Pharmacare Program beneficiaries.

Dose	2006	2007	2008	2009	2010	2011
≤1.2 mg, no. (%)	86 (63.7)	145 (72.1)	175 (65.8)	199 (67.5)	206 (61.3)	63 (67.0)
≤1.5 mg, no. (%)	94 (69.6)	148 (73.6)	180 (67.7)	206 (69.8)	213 (63.4)	65 (69.1)
>1.5 mg, no. (%)	41 (30.4)	53 (26.4)	86 (32.3)	89 (30.2)	123 (36.6)	29 (30.9)
Total	135	201	266	295	336	94

Values may not sum 100% as patients in the ≤1.2 group may have also been captured in the ≤1.5 group.

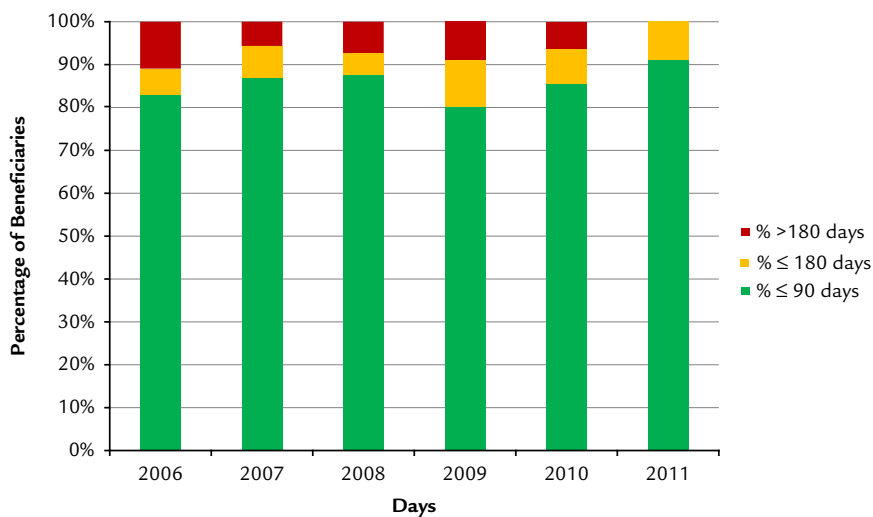


Figure 1. Proportion of Nova Scotia Seniors' Pharmacare Program beneficiaries by colchicine duration and year.

The cost of colchicine for patients taking 1.2 to 1.8 mg for 1 to 3 days, followed by 0.6 mg orally, is ~Can\$20 to Can\$28 for a 30-day supply.²¹ Appropriate use of colchicine at lower doses and for

shorter durations has the potential for cost savings to the NSSPP, private drug plans, and individual patients, but any economic analysis must also account for the health consequences of changing prescribing behaviors.

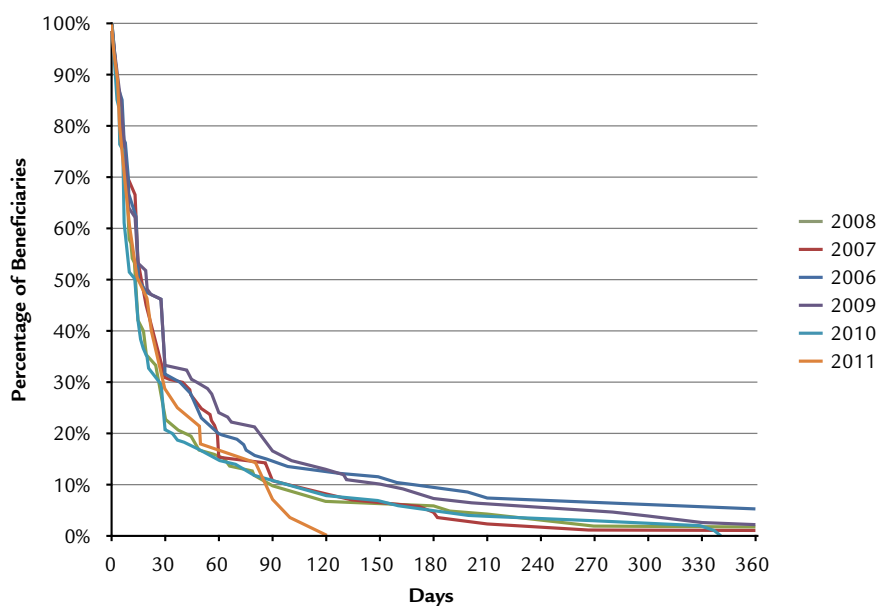


Figure 2. Cumulative days of colchicine use by calendar year (April 1, 2006 to March 31, 2011) in Nova Scotia Seniors' Pharmacare Program beneficiaries for first treatment course per year.

Clinical Therapeutics

Table III. Patient descriptors and duration of colchicine use (>90 days and >180 days) based on multivariate logistic regression.

	Colchicine Duration	
	> 90 days	> 180 days
Per calendar year	0.967 (0.876–1.066)	1.021 (0.913–1.142)
Per 5-year increase in age	1.083 (0.975–1.205)	1.029 (0.912–1.160)
Women (vs men)	0.737 (0.548–0.992)*	0.814 (0.580–1.142)

Values are expressed as odds ratio (95% CI).

*Significant at 0.05 level.

Such an analysis was beyond the scope of this study, but future work should examine the cost effectiveness of implementing these guidelines.

Limited data on appropriateness of colchicine in treatment of gout are reported in the literature. In a study of hospitalized patients treated for acute gout, 26% were considered to be receiving an inappropriate mean initial colchicine dose of >1.5 mg/d. Patients who received higher mean doses and longer durations of therapy had an increased risk of diarrhea.²² Although we were unable to differentiate between acute and chronic gout, similarly in our study, approximately one-quarter of patients with gout received mean doses of colchicine >1.5 mg.

A retrospective review that evaluated colchicine prescribing for prevention of acute gout in an out-patient primary care setting reported inappropriate use by 73.8% of the study population.²³ Patients in that study received lower mean doses of colchicine (0.6 mg/d) as prophylaxis than our study population. However, patients in both the appropriate and inappropriate arms received extended durations of treatment (median, 1.12 years and 3.26 years, respectively).²³ Limited data support the optimal duration of colchicine prophylaxis when initiated in combination with ULT to prevent acute gout attacks; however, like a proportion of patients in our study, patients in both appropriate and inappropriate arms exceeded current ACR guidelines and STOPP criteria recommendations for

the duration of colchicine use.²³ Extending treatment durations may lead to continued risk of adverse effects, a higher pill burden, and increased costs to patients or the health care system.

Development of a protocol to guide treatment of gout may improve adherence to guidelines and STOPP criteria. Kamalaraj et al²⁴ studied the effect of implementing a protocol for the treatment of gout in hospitalized patients. The protocol targeted non-rheumatologists and was implemented with a variety of formats, including wall posters depicting the protocol in words, educational sessions led by rheumatologists, and a link on the hospital's intranet (triggered when a serum urate concentration was ordered). Their results found that 22.1% of patients in the preprotocol group were prescribed inappropriate doses of colchicine (>1.5 mg/d) compared with only 1.5% of patients in the post-protocol group ($P < 0.001$). The number of adverse events also decreased from 28% before the protocol to 13.5% after the protocol ($P < 0.01$).²⁴ In that study, approximately one-quarter of patients were prescribed high-dose colchicine by non-rheumatologists.

Implementing simple, evidence-based clinical decision support tools for colchicine dose and duration through information technology used by general practitioners may be an additional strategy to improving practice.^{25–27} Clinical decision support tools, which include information on recommended colchicine dose and duration, could be incorporated into electronic health records used by general practitioners. The more specific and directed the tool is, the more successful the intervention in affecting prescribing behaviors.²⁸

Our study has several strengths. It provides 5-year data of a large population. As recommended by Johnson et al,²⁹ we implemented incident user design, which identified patients who were newly prescribed medications for management of gout. This strategy minimizes bias that results from comparisons of new patients with patients who have been on the medication before the start of the study and captures all events that occurred after the initiation of treatment.²⁹

A number of limitations should be considered. The NSSPP data include only beneficiaries eligible and registered in the program and does not capture data for patients aged ≥ 65 years who may pay out of pocket or are covered by private drug insurance companies. It does not separately report on the $\sim 7.5\%$ of the population who reside in long-term

care. In addition, administrative prescription data were not linked to other health records or patient reported outcomes, and we are limited in our ability to identify the type and clinical characteristics of gout or to follow patients to monitor benefit or harm. We were also unable to determine contraindications to ULT or nonsteroidal anti-inflammatory drugs, which may require lengths of colchicine therapy >6 months.² Other limitations include an inability to determine use of colchicine through prescription drug samples or to identify patients for whom the drug was prescribed and not dispensed. Finally, we were unable to assess patient adherence to recommended therapy.

Generalizability of results should also be considered. Almost one-half of our study population were women; however, gout has been shown to occur more commonly in men than women in the general population. In those aged 70 to 79 years, population estimates report that 10.8% of men compared with 4.6% of women have experienced gout.¹ Despite these limitations, our results provide insight into prescribing practices of physicians for management of gout in older persons.

CONCLUSIONS

Our findings are the first to report on colchicine dose and duration with the use of STOPP criteria in a specific cohort of older persons with incident gout. At the end of the study period, the number of older persons dispensed potentially inappropriate colchicine doses (>1.2 mg/d) and extended durations (>3 months) remained high (27.9%–38.7% per year and 14.2%, respectively) despite new evidence. Academic detailing programs and clinical decision support tools directed to general practitioners and other prescribers are needed to improve colchicine dosing and duration. Future research should focus on evaluation of implemented interventions and completion of real-world studies to examine the optimal length for prophylactic use of colchicine so patients are not continued on therapy indefinitely. Finally, appropriate use of colchicine may result in cost savings to insurers and patients.

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CONFLICTS OF INTEREST

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Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

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