Androgen deprivation therapy for prostate cancer: Prescribing behaviors and preferences among urologists

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Abstract

Introduction: Several androgen deprivation therapy (ADT) medications are available for treating advanced prostate cancer with roughly equivalent oncological efficacy and tolerability. We investigated the proportion of physicians who predominantly prescribe one type of ADT drug ("mono-prescriber") and assessed characteristics associated with prescription behavior.
Methods: Ontario men aged ≥65 years who were diagnosed with advanced prostate cancer (1997–2017) and initiated ADT thereafter for ≥3 consecutive months were identified using

population-level administrative data. Their first prescription for injectable ADT was linked to a physician, and urologists with ≥10 prescriptions over the study period were included in the analysis (n=282). Urologists were classified as high mono-prescribers if ≥80% of their prescriptions were for one drug type. Multivariable logistic regression was used to examine the association of physician characteristics with the odds of being a high mono-prescriber.
Results: Overall, 67 (23.8%) of urologists were classified as high mono-prescribers but the frequency varied across health planning regions. The most commonly prescribed drugs and those used by mono-prescribers were goserelin (41.8% and 56.7%) and leuprolide (44.3% and 43.3%), respectively. In multivariable analysis, the odds of a physician being a high mono-prescriber were higher with more years in practice (odds ratio [OR] 1.06/ year, 95% confidence interval [CI] 1.03–1.09, p<0.0001) and lower for higher patient volume (OR 0.33 for above vs. below median, 95% CI 0.17–0.63, p=0.0008).
Conclusions: Overall, one in four urologists were classified as high mono-prescribers. Mono-prescribers had more years in practice and smaller volume practices, potentially suggesting habitual prescription behavior and/or the effect of external pressures.

Introduction

Rather than selecting medications equally and at random from a range of options within a therapeutic class, physicians often prescribe within a narrow range of "preferred" drugs.[1] While some instances of drug preference are indicated by clinical efficacy (i.e. therapeutic superiority or avoidance of adverse effects) or cost-effectiveness (e.g. generic drugs), there is concern that prescription choice may reflect habitual prescribing, and/or external influences such as pharmaceutical marketing.[1-3]

In the context of androgen deprivation therapy (ADT) for advanced prostate cancer (PCa), several gonadotropin releasing hormone (GnRH)-agonist and antagonist medications are available in Canada, with similar oncological efficacy and tolerability for the average patient.[4, 5] Given few clinical indications to prescribe one drug over another, ADT prescription practices serve as a relatively ideal natural experiment to explore variability in and drivers of prescriber practice within urologists. Empirical evidence on prescribing behavior is limited, and to our knowledge, there are no studies examining prescriber practices for ADT in Canada. Therefore, using population-level administrative data, we investigated the proportion of physicians who predominantly prescribe one type of drug (i.e. "mono-prescriber" behaviour) for ADT in advanced PCa patients and explored the physician and patient characteristics associated with prescribing behaviour.

Methods

Overview

The population-level administrative and registry data at ICES (Ontario, Canada; population 14 million) are well described.[6-8] Medical care is reimbursed through a single, government funded health insurance system (Ontario Health Insurance Plan [OHIP]) with prescription medication benefits provided to all individuals over age 65 (Ontario Drug Benefit [ODB]). The Ontario Cancer Registry captures 93% of PCa diagnoses within the province.[9] These datasets were linked using unique encoded identifiers and analyzed at ICES. The study was approved by the University Health Network Research Ethics Board (18-6261).

Patients

Men in Ontario diagnosed with PCa (International Classification of Diseases [ICD]: ICD-O-3 C61.9, ICD-10 C61, ICD-9 185) between 1997–2017, and initiated ADT for a minimum of 3 consecutive months were included.[7]

Prescriptions

We only included the first injectable ADT prescription in the ODB for each patient as subsequent scripts (i.e. prescription refills) likely represent the same medication and may not be indicative of prescriber preference. As the ODB database is limited primarily to patients over 65, our cohort was restricted to these individuals.

Physicians

We aimed to assign each ADT prescription to a staff/attending physician, rather than the prescriber listed in the ODB who may be a resident or fellow. Although residents and fellows are involved in the delivery of care (i.e. prescriptions), they remain supervised by an attending staff physician (re: treatment intent) and could not be interpreted as a distinct group. Furthermore, it allowed for better distinction of PCa case volume and the identification of specialty (not assigned for residents and fellows until certification).

Each ADT prescription was linked to attending staff using billed OHIP PCa-related consultations within 30 days of prescription. If a prescription was linked to more than one consultation, the most-commonly associated physician was assigned. In the case of a tie, we selected an oncologist (defined as urologist, radiation oncologist or medical oncologist, internal medicine and hematology) associated with the first (earliest) consultation. We excluded physicians with less than 10 prescriptions over the study period to provide a reasonable number of prescriptions to assess prescribing patterns.

Classification of high mono-prescribers

Each prescription was assigned to a medication (buserelin, leuprolide, goserelin, triptorelin, or degarelix; based on drug identification number). Notably, buserelin, goserelin, and leuprolide

have been available in Ontario since 1996/1997, while triptorelin and degarelix became available in 2007 and 2011, respectively (Figure 1). Additionally, we divided the leuprolide category into Lupron and Eligard (available since 2004).

For each physician, we calculated the number and percentage of each medication to identify the medication with the maximum percentage prescription. For example, for a physician who prescribed leuprolide for 85% of prescriptions and triptorelin for 15% of prescriptions, the maximum percentage would be 85% and assigned drug type would be leuprolide. The main outcome was a binary variable classifying physicians as high mono-prescribers or not, based on this maximum percentage. A threshold of 80% was used to classify physicians as high mono-prescribers, with a 90% cut-off in sensitivity analysis. As these have not been previously documented in the literature, these thresholds were selected to represent those considered much more extreme than expected by chance alone and hypothesized to represent a strong preference for a drug.

Covariates

Physician characteristics

Medical specialty, sex, and graduation year were obtained from the ICES Physician Data Base. Years in practice was the difference between the first prescription in the dataset and MD certification.

Patient volume was defined as the number of PCa patients in the cohort treated per physician over the study period and was operationalized at the median for analysis.

We assigned physicians to the institution type most-commonly associated with their OHIP billings (for the study period's prescription history) into: (i) academic, (ii) regional cancer-centre, and (iii) other (e.g. community hospital).

Patient characteristics

Average age, income quintile, rurality, and comorbidity index (Adjusted Clinical Groups [ACG] score, 2 year lookback) at first prescription were calculated for all patients associated with each physician. ACG score was derived using the John Hopkins ACG® System Aggregated Diagnosis Groups (V10; excluding malignancy).[10]

Statistical analysis

The prescribing physician was the unit-of-analysis. Physician and patient characteristics were compared between those who were high mono-prescribers and those who were not by using Chi-square or Fisher's exact test for categorical variables, and t-tests or Wilcoxon rank-sum for continuous variables, as appropriate. Multivariable logistic regression was used to examine the association of physician characteristics with being a high mono-prescriber. A p-value of <0.05

indicated statistical significance (two-tailed comparison). Analyses were completed using SAS Statistical Software V9.4.

Because the availability of ADT drugs in Ontario changed over time, we additionally performed a sensitivity analysis which included only prescriptions filled from 2009+, as all drug types (except for degarelix) were available and had reached a level of market penetration/stability by that time. We limited the cohort to urologists to allow for a clean and focused main analysis; however, all specialties were examined in a sensitivity analysis.

Results

Between July 1997–December 2017, 52,385 patients were diagnosed with PCa and had ≥1 prescription for injectable ADT in the ODB (Supplemental Figure). An attending PCa physician could be assigned for 45,722 patients (87%), resulting in 840 unique physicians. After excluding physicians with <10 prescriptions, 430 physicians remained, of which 282 were urologists.

When assessing the maximum percentage prescription for each prescriber, the predominant drug represented 65.8% (range: 35.1-100.0%; IQR: 52.3-78.2%) of first prescriptions amongst urologists. Drug type for the maximum percentage was mainly goserelin (41.8%) and leuprolide (44.3%); with the remaining distributed between buserelin (5.9%), degarelix (3.8%), triptorelin (4.2%), or more-than-one (1.2%). Within leuprolide, 30.9% and 13.4% of maximum prescriptions were Lupron and Eligard, respectively. Figure 1 depicts the year-to-year prescription trend for each ADT drug, including their pertinent approvals in the Ontario Formulary.

Based on the 80% cut-off, 67 of 282 urologists (23.8%) were classified as high mono-prescribers. The most common drugs used by mono-prescribers were goserelin (38, 56.7%) and leuprolide (29, 43.3%). Leuprolide mono-prescribers almost exclusively prescribed Lupron (24-28) versus Eligard (1-5, small cells suppressed for identification). Based on the 90% cut-off (sensitivity analysis), 36 of 282 urologists (12.8%) were classified as high mono-prescribers.

High mono-prescribers were older (52 vs 38 years; $p<0.001$), had practiced longer (25 vs 11 years; $p<0.001$), had a smaller patient volume (42 vs 81 patients; $p<0.001$), and were less likely to be Canadian medical graduates (69.7% vs 84.1%; $p=0.009$) (Table 1A). There were no significant differences in physician sex, year of prescription, or institution type. The percentage of high mono-prescribers varied from 0% to 45% across the 14 Ontario health planning regions, although the differences were not statistically significant ($p=0.12$). There were no significant differences in the characteristics of patients treated by non-high versus high mono-prescribers (Table 1B).

The variables of physician age, years in practice, and year of first prescription were highly correlated and only years in practice was included in the multivariable logistic regression models along with sex, Canadian Medical Graduate status, institution type and patient volume (Table 2). In multivariable analysis, the odds of being a high mono-prescriber were higher with

more years in practice (OR 1.06/year, 95%CI 1.03-1.09, p<0.0001) and lower for higher patient volume (OR 0.33 for those above vs below median, 95%CI 0.17-0.63, p=0.0008).

Results were very similar in sensitivity analyses assessing prescriptions filled after 2009 and a 90% threshold for mono-prescription. After 2009, a similar proportion of mono-prescribers (51/221, 23.1%) and drug type (56.9% leuprolide [of which about 90% was Lupron], 43.1% goserelin) was observed. In both analyses, greater years in practice and patient volume remained significantly associated with being a mono-prescriber [Supplemental Tables 1-4].

In the cohort not limited to urologists, urologists were the most common prescriber of ADT (66%), followed by radiation oncologists (27%) and medical oncologists (7%). In multivariable analysis, the estimate of the odds of being a mono-prescriber was higher for radiation oncologists versus urologists (1.81 (95%CI 0.91-3.61), p=0.09), but not statistically significant (Supplemental Table 5). The association of other covariates with the odds of being a high mono-prescriber in the larger cohort was similar to that of the main analysis (urologists only).

Discussion

Using population-level administrative data to assess first ADT prescriptions, we found that nearly 1-in-4 urologists demonstrated a strong preference for a single medication with mono-prescription >80% of one drug therapy. Remarkably, when this threshold was raised to >90% indicating mono-prescriber behaviour, 1-in-8 urologists continued to predominantly use one medication to the exclusion of others. We selected ADT as a relatively-ideal natural experiment to investigate prescription practices as no medication demonstrates a substantial clinical advantage for the typical patient over another (beyond monthly GnRH antagonist dosing for rapid castration, etc.[4, 5]; although this represented only a small subset (2.5%) of prescriptions). Indeed, there were notably no differences in the characteristics of patients treated by high mono-prescribers versus those who were not, or with regards to institution type.

Although no strict guidance exists to constitute mono-prescriber behaviour within this setting (either within hormonal therapy or amongst urologist prescribers), we believe that these results are much more extreme than those expected by chance only. This may represent the potential for (undue) influence within our health system and physicians may be subject to non-clinical external pressures to prescribe one drug therapy over another.[4] For example, these findings may represent conscious and intentional (e.g. overt influence), conscious and unintentional (e.g. busy clinic and prescribing a "go-to" medication), or subconscious (e.g. reciprocity) forms of bias, potentially representing influences such as pharmaceutical marketing, differences in physician comfort and training with medication. It should also be noted that mono-prescribing based on greater familiarity with a drug could benefit patients through improved drug administration practices, improved recognition and treatment of side effects and better patient counselling.

For context, other studies assessing the prevalence of comparable behaviours across general practitioners, internists, and all-comer physicians suggest that this issue is more pervasive for certain drug classes versus others. In an analogous analysis of initial prescriptions across 10 therapeutic classes[1], the percentage of physicians prescribing only a single drug ranged from less than 1% (selective serotonin reuptake inhibitors), to 2-4% (statins, proton pump inhibitors, channel blockers, beta blockers), to 6-10% (antihistamines, antidiabetic, non-steroidal anti-inflammatory drugs), and up to 15% (angiotensin-converting enzyme inhibitors and opioids). Notably, the preferred "favourite" drugs identified were predominantly the most heavily advertised or promoted therapy at the time.

Furthermore, we observed substantial regional variation (0%–45%) across the different health planning regions of Ontario, although this was not statistically significant overall. Geographical variation may indicate discrepancies in pharmaceutical advertisement/coverage, local practices and training. While the limits of administrative data prevent further assessment, more granular data including pharmaceutical coverage and promotion, geographic and time trends are needed to assess these practice patterns more thoroughly.

Other explanations may lie in the practical availabilities of medications, their ease of delivery, and the likelihood of habitual prescription. The majority of mono-prescription medications were either goserelin or leuprolide which were available since 1996/1997. Given that physicians who were older/with greater years in practice and those with lower volume practices were more likely to be mono-prescribers in our results, this may represent physicians who are more likely to be habitual prescribers of medications that they have greater familiarity or longer experience with. Conversely, newer medications (e.g. triptorelin) may not have gained as much market share versus the established medications in Ontario.

Moreover, formulation and preparation are important logistical considerations in clinical practice.[5] Some formulations are ready to use out of the box, whereas others require reconstitution (mixing) in clinic and/or refrigeration. In a busy clinical setting, this may impede providers as they are more onerous to administer. Furthermore, salient details such as subcutaneous versus intramuscular administration and needle gauge size, and cost[11] represent other important patient-driven considerations. Finally, differences in dosing frequency can affect visits, billing, and opportunities to follow-up.

Ultimately, these findings highlight the complex nature of medication prescription practices with clear implications for patients and clinical care. Although ADT does not demonstrate substantial efficacy differences between medications, these same potential internal and external forces may influence the decision-making behind other medications where the stakes are much higher such as the prescribing of opioid or non-opioid analgesia. Awareness is the first step, and further research to explore these relationships, their sources, and interactions is needed.

Limitations

Given the limitations of the administrative data, several pragmatic decisions had to be made. Firstly, no clear threshold exists to inform what constitutes mono-prescription of ADT, so we empirically selected a threshold of 80% following clinical consultation. However, we feel our results are likely robust to this assumption, with similar predictors and trends maintained across a more-stringent sensitivity analysis. Secondly, patient preferences are not captured within administrative data, although these play a small role in the selection of specific prescriptions based on our clinical experience. Similarly, prescription intent by the physician was inferred by restricting the analysis to the first script only; refill/subsequent prescriptions are likely not indicative of true preference. However, this may misclassify and omit a small number of cases where individuals switch therapies or providers. Thirdly, not all patient covariates (e.g. Gleason score) were included; although notably, none of the patient covariates studied were significantly different. Given the relative clinical equivalence of all medications, we predominantly focused on describing the demographic- and physician-level predictors of prescribing practices in this study. Finally, we decided to match prescriptions to attending staff. This allowed more delineation of provider characteristics but may misattribute the prescribing preferences (and influence thereof) of learners.

Conclusions

We observed that 1-in-4 urologists were mono-prescribers at a threshold of >80% prescriptions for a single ADT medication type. Mono-prescribers were older with more years in practice and had smaller volume practices, in addition to substantial regional variation, potentially suggesting habitual prescription and/or external pressures independent of patient and institution characteristics. This research highlights the high prevalence of mono-prescription amongst urologists, and the need for further research into the mechanistic drivers in selecting a "favourite" drug therapy, both within ADT and beyond.

Role of the Funding Source. The funding source had no role in study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the article for publication.
Availability of data and material. The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS.
Code availability. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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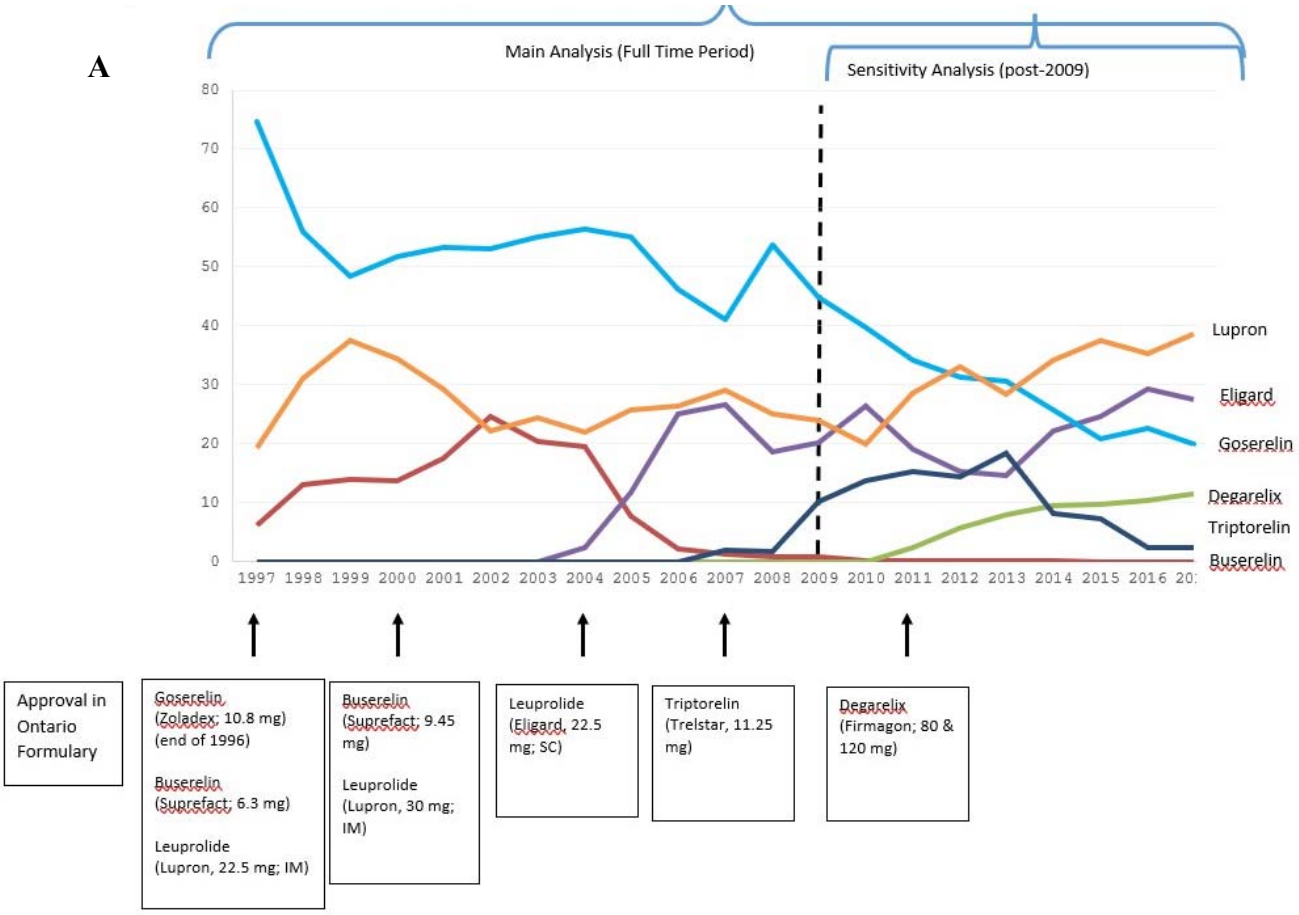
Figures and Tables

Figure 1. Proportion of androgen deprovation therapy drug type prescibed by year.
(A) Depicts the year-to-year trend in prescriptions for each ADT drug type, including their pertinent date of approval in the Ontario Drug Formulary. Lupron and Eligard are shown separately.
(B) contains similar information, but Lupron and Eligard are combined as leuprolide.



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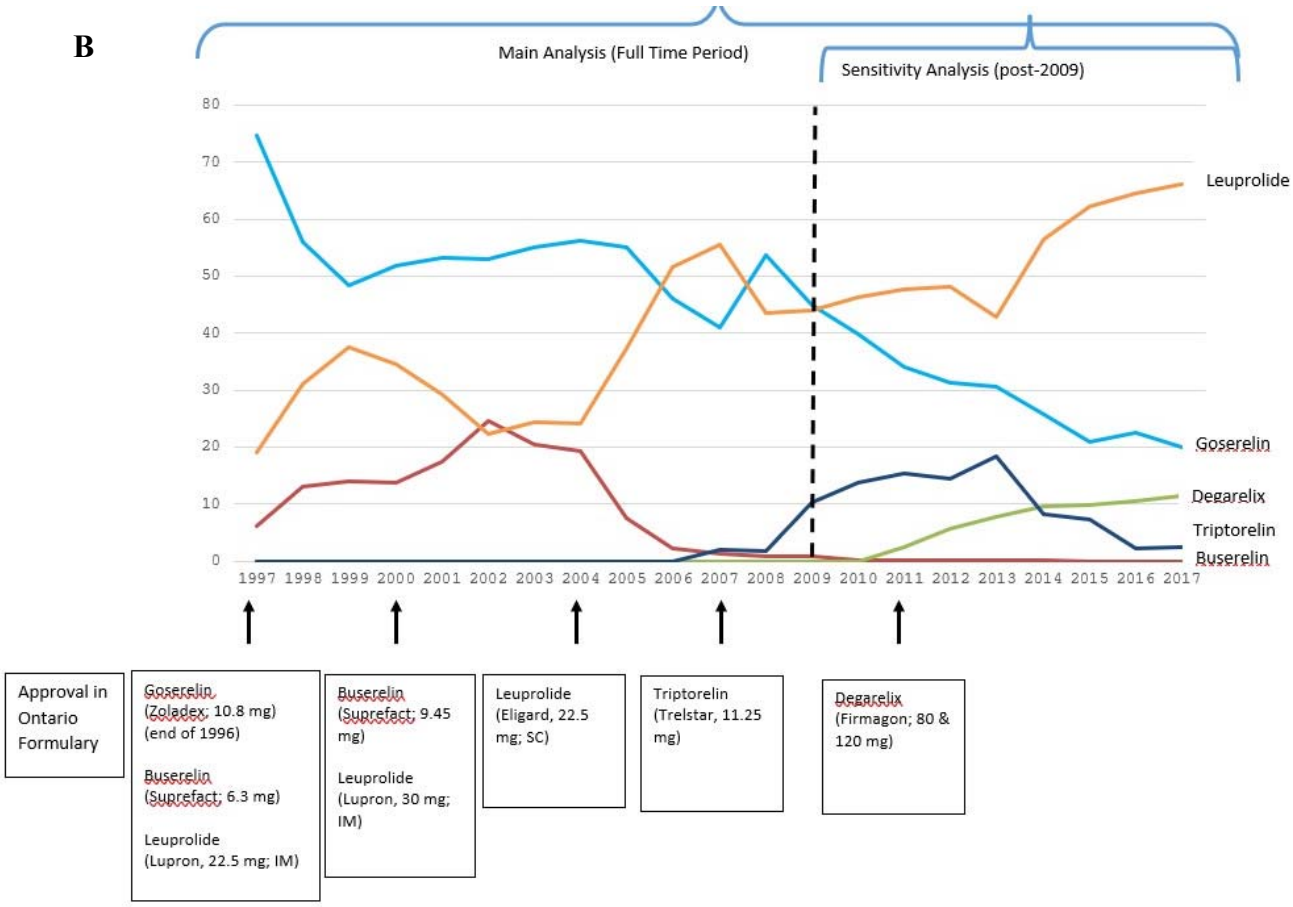

Table 1. Characteristics of low and high mono-prescriber urologists (80% cutoff) and their patients

A. Urologist (provider)[a] characteristics

Characteristic	All urologists n=282	Low mono-prescriber n=215	High mono-prescriber n=67	p[b]
Age (years), median (IQR)	40 (34–53)	38 (34–48)	52 (36–62) 52.00 (36.00–62.00)	<0.001
Sex, n (%) Female Male	7 (2.5%) 275 (97.5%)	2–6[c] 207–211	1–5 64–68	0.6
Years in practice (years), median (IQR)	13.5 (7–27)	11 (7–21)	25 (8–38)	<0.001

Year of first prescription, median (IQR)	1998 (1997–2005)	1999 (1997–2006)	1998 (1997–2002)	0.3
Number of patients per urologist, median (IQR)	57.5 (32–132)	81 (38–143)	42 (19–84)	<0.001
Canada medical graduate, n (%) No Yes	 54 (19.3%) 226 (80.7%)	 34 (15.9%) 180 (84.1%)	 20 (30.3%) 46 (69.7%)	 0.009
Type of institution, n (%) Academic Regional cancer center Other	 85 (30.6%) 29 (10.4%) 164 (59.0%)	 61 (28.8%) 23 (10.9%) 128 (60.4%)	 24 (36.4%) 6 (9.1%) 36 (54.6%)	 0.5
B. Patient[d] characteristics				
Characteristic	**All urologists n=282**	**Low mono-prescriber n=215**	**High mono-prescriber n=67**	**p**
Age (years), median (IQR)	75.9 (74.8–77.1)	75.9 (74.7–77.1)	75.9 (74.8–77.2)	0.6
ACG score, mean (SD)	9.4 (0.8)	9.5 (0.8)	9.5 (1.0)	0.9
ACG score, median (IQR)	9.5 (0.9–10.0)	9.5 (9.1–9.9)	9.5 (8.8–10.1	0.8
Income quintile[e], n (%) 2–2.5 3–3.5 4–4.5 5	 55 (19.5%) 177 (62.8%) 49 (17.4%) 1 (0.4%)	 44 (20.5%) 135 (62.8%) 35 (16.3%) 1 (0.5%)	 11 (16.4%) 42 (62.7%) 14 (20.9%) 0 (0%)	 0.2
Rural, n (%) Yes No	 20 (7.1%) 262 (92.9%)	 13 (6.1%) 202 (94.0%)	 7 (10.6%) 60 (89.6%)	 0.4

[a]Based on the date of their first prescription. [b]p-value comparing low and high mono-prescribers. [c]Actual numbers suppressed due to small cell size. [d]Calculated the average value for patients per physician to derive one value for each physician. [e]Categories are reported per physician (i.e., median income quintile (1–5) per patient was calculated and summated into the median patient-value per physician). ACG: Adjusted Clinical Groups; IQR: interquartile range; SD: standard deviation.

Table 2. Factors associated with high mono-prescriber urologists (80% cutoff)				
Characteristic		**OR**	**95% CI***	**p**
Sex	Male Female	1.0 0.59	 0.07–5.20	 0.6
Canadian medical graduate	No Yes	1.0 1.20	 0.56–2.60	 0.6
Years in practice	Per year	1.06	1.03–1.09	<0.0001
Institution type	Academic (Ref) Cancer center Community	1.0 0.75 0.60	 0.24–2.29 0.31–1.17	 0.6 0.13
Patient volume	Below median (ref) Above median	1.0 0.33	 0.17–0.63	 0.0008

CI: confidence interval; OR: odds ratio.