

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

Douglas C. Cheung¹, Lisa J. Martin², Shabbir M.H. Alibhai³, Maria Komisarenko², Christoffer Dharma⁴, Yue Niu⁴, Padraig Warde⁵, Srikala S. Sridhar⁶, Neil E. Fleshner^{1,2}, Girish S. Kulkarni^{1,2}, Antonio Finelli^{1,2}

¹Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada; ²Division of Urology, Department of Surgical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; ³Department of Medicine, University Health Network, University of Toronto, Toronto, ON, Canada; ⁴ICES, Toronto, ON, Canada; ⁵Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; ⁶Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Cite as: Cheung DC, Martin LJ, Alibhai SMH, et al. Androgen deprivation therapy for prostate cancer: Prescribing behaviors and preferences among urologists. *Can Urol Assoc J* 2022;16(10):351-7. <http://dx.doi.org/10.5489/cuaj.7730>

Published online May 20, 2022

Appendix available at cuaj.ca

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 among 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” behavior) for ADT in advanced PCa patients and explored the physician and patient characteristics associated with prescribing behavior.

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 and 2017, and initiated ADT for a minimum of three 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 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% cutoff 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 Database. 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 1) academic; 2) regional cancer center; and 3) other (e.g., community hospital).

Patient characteristics

Average age, income quintile, rurality, and comorbidity index (Adjusted Clinical Groups [ACG] score, two-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-squared 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 com-

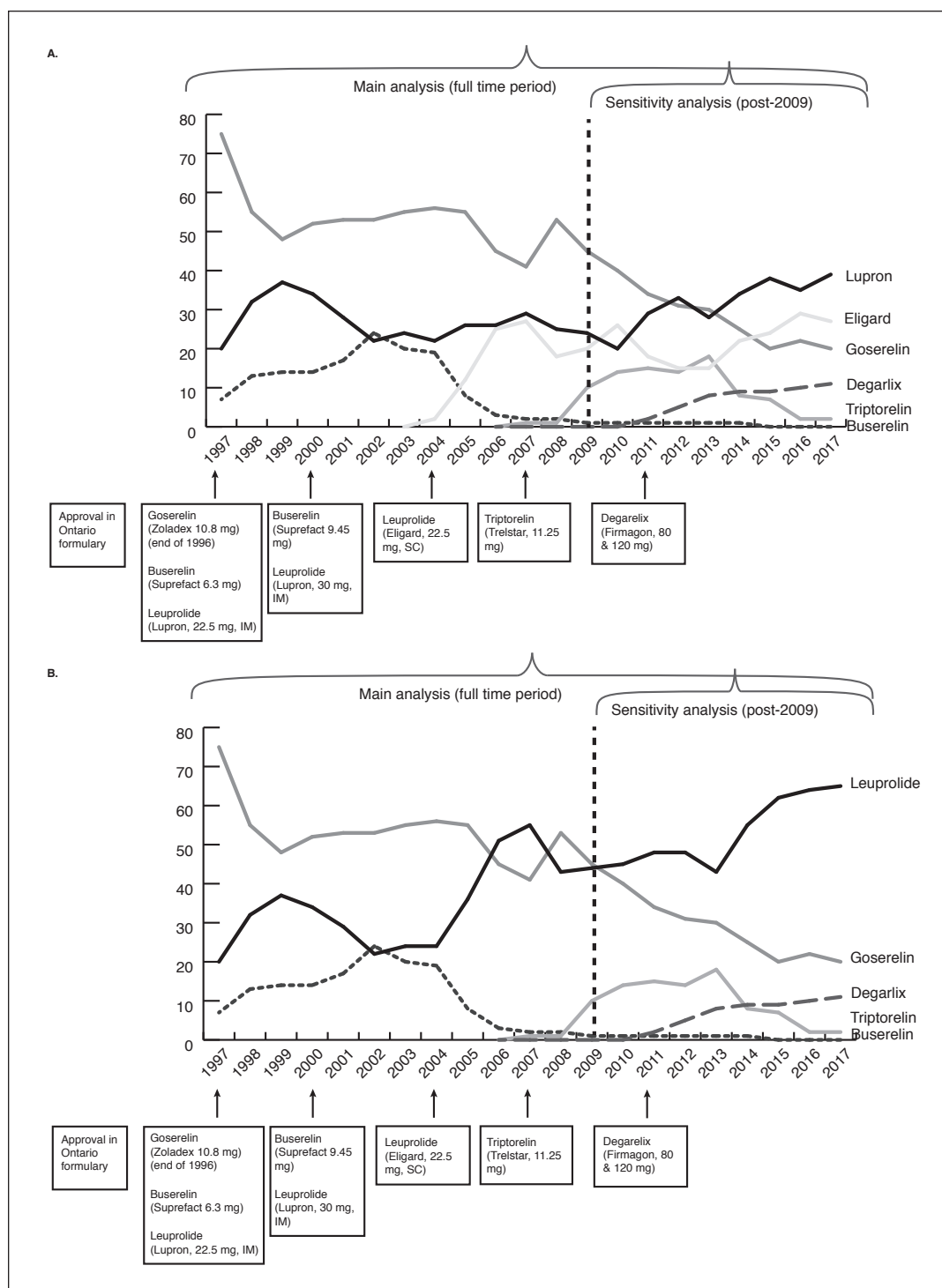


Figure 1. Proportion of androgen deprivation therapy (ADT) drug type prescribed by year. **(A)** Depicts the year-to-year trend in prescriptions for each ADT drug type, including their pertinent date of approval in the Ontario Drug Formulary. Lupron and Eligard are shown separately. **(B)** contains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

parison). 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

that included only prescriptions filled from 2009 onwards, 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 and December 2017, 52 385 patients were diagnosed with PCa and had ≥ 1 prescription for injectable ADT in the ODB (Supplementary Figure 1; available at cuaj.ca). 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%, interquartile range [IQR] 52.3–78.2%) of first prescriptions among 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 the leuprolide group, 30.9% and 13.4% of maximum prescriptions were for 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% cutoff, 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) vs. Eligard (1–5, small cells suppressed for identification). Based on the 90% cutoff (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 0–45% 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 vs. 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 (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 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 (Supplementary Tables 1–4; available at cuaj.ca).

In the cohort not limited to urologists, urologists were the most common prescribers 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 vs. urologists (1.81, 95% CI 0.91–3.61, $p = 0.09$) but not statistically significant (Supplementary Table 5; available at cuaj.ca). 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 one in four 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 behavior, one in eight 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 vs. those who were not, or with regards to institution type.

Although no strict guidance exists to constitute mono-prescriber behavior within this setting (either within hormonal therapy or among 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,

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)	<0.001
Sex, n (%)				
Female	7 (2.5%)	2–6 ^c	1–5	0.6
Male	275 (97.5%)	207–211	64–68	
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	54 (19.3%)	34 (15.9%)	20 (30.3%)	0.009
Yes	226 (80.7%)	180 (84.1%)	46 (69.7%)	
Type of institution, n (%)				
Academic	85 (30.6%)	61 (28.8%)	24 (36.4%)	0.5
Regional cancer center	29 (10.4%)	23 (10.9%)	6 (9.1%)	
Other	164 (59.0%)	128 (60.4%)	36 (54.6%)	
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	55 (19.5%)	44 (20.5%)	11 (16.4%)	0.2
3–3.5	177 (62.8%)	135 (62.8%)	42 (62.7%)	
4–4.5	49 (17.4%)	35 (16.3%)	14 (20.9%)	
5	1 (0.4%)	1 (0.5%)	0 (0%)	
Rural, n (%)				
Yes	20 (7.1%)	13 (6.1%)	7 (10.6%)	0.4
No	262 (92.9%)	202 (94.0%)	60 (89.6%)	

^aBased on the date of their first prescription. ^bp-value comparing low and high mono-prescribers. ^cActual numbers suppressed due to small cell size. ^dCalculated the average value for patients per physician to derive one value for each physician. ^eCategories 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.

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 behaviors across general practitioners, internists, and all-comer physicians suggest that this issue is more pervasive for certain drug classes vs. 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, nonsteroidal anti-inflammatory drugs), and up to 15% (angiotensin-converting enzyme inhibitors and opioids). Notably, the preferred “favorite” 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 pharmaceuti-

Table 2. Factors associated with high mono-prescriber urologists (80% cutoff)

Characteristic		OR	95% CI	p
Sex	Male	1.0		
	Female	0.59	0.07–5.20	0.6
Canadian medical graduate	No	1.0		
	Yes	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)	1.0		
	Cancer center	0.75	0.24–2.29	0.6
	Community	0.60	0.31–1.17	0.13
Patient volume	Below median (ref)	1.0		
	Above median	0.33	0.17–0.63	0.0008

CI: confidence interval; OR: odds ratio.

cal 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. Most mono-prescription medications were either goserelin or leuprolide, which have been 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 vs. 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 vs. intramuscular administration, needle gauge size, and cost,¹¹ represent other important patient-driven considerations. Finally, differences in dosing frequency can affect visits, billing, and opportunities for followup.

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 one in four 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 among urologists and the need for further research into the mechanistic drivers in selecting a “favorite” drug therapy, both within ADT and beyond.

Competing interests: Dr. Sridhar has been an advisory board member for AstraZeneca, Astellas, Bayer, BMS, Immunomedex, Janssen, Merck, Pfizer, Roche, and Seagen. Dr. Fleshner reports grants from Astellas, Bayer, Janssen, Nucleix, Progenix, and Sanofi; consulting fees from AbbVie, Amgen, Astellas, Bayer, Ferring, Janssen, and Sanofi; honoraria from Ferring; support for meetings and travel from UCLA Department of Urology, University San Raffaele, Bayer, Jo-Events, Tecnofarma Prostate Forum, and Janssen; a leadership/fiduciary role in Verity Pharmaceuticals and POINT Biopharma; and stock/stock options in Verity Pharmaceuticals and POINT Biopharma. Dr. Kulkarni has been an advisory board member for Astellas, BMS, EMD Serono, Ferring, Janssen, Merck, Roche, Theralase, and Verity; has received grants/honoraria from AbbVie, AstraZeneca, Ferring, Sanofi, and TerSera; and has participated in clinical trials supported by AstraZeneca, BMS, Janssen, Merck, Pfizer, Seagen, Theralase, and Verity. Dr. Finelli has been a consultant and participated in advisory boards for AbbVie, Amgen, Astellas, Ferring, Hoffman-LaRoche, Ipsen, Janssen, Sanofi Pasteur, and Tesaro; and has participated in clinical trials supported by AstraZeneca, Medivation, Merck, and Pfizer. The remaining authors do not report any competing personal or financial interests related to this work.

Acknowledgements/funding: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This study also received funding from the Princess Margaret Cancer Foundation. Parts of this material are based on data and information compiled and provided by the MOH and the Canadian Institute for Health Information. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this material are based on data and information provided by Ontario Health (OH). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of OH. No endorsement by OH is intended or should be inferred. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File.

This paper has been peer-reviewed.

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Correspondence: Dr. Antonio Finelli, University Health Network/Princess Margaret Cancer Centre, Toronto, ON, Canada; Antonio.Finelli@uhn.ca