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ORIGINAL ARTICLE

Factors that may be influencing the rise in prescription testosterone replacement therapy in adult men: a qualitative study

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Abstract

Objective: To explore and describe the factors that may be influencing the rise of prescribing and use of testosterone replacement therapy (TRT) in adult men.
Design: A rapid qualitative research design using semi-structured interviews with providers and patients.
Setting: Ontario, Canada.
Participants: Nine men who have used TRT (referred to as ''patients''), and six primary care clinicians and seven specialists (collectively referred to as ''providers'') who prescribed or administered TRT.
Method: Patients' and providers' perspectives were investigated through semi-structured interviews. A purposive sampling approach was used to recruit all participants. We conducted qualitative analysis using the framework approach for applied health research.
Main findings: Participants perceived the following factors to have influenced TRT prescriptions and use in adult men: provider factors (diagnostic ambiguity of age-related hypogonadism and beliefs about appropriateness of TRT) and patient factors (access to information on TRT and drug seeking behavior). They perceived that these factors have perpetuated a rise in prescription in the absence of clear clinical guidelines and unclear research evidence on the safety and efficacy of TRT.
Conclusion: The findings of this study highlight that much work still needs to be done to improve diagnostic accuracy and encourage appropriate TRT prescription in adult men. In addition, both patients and providers need more information about the risks and long-term effects of TRT in men.

Keywords

Testosterone replacement therapy, androgen therapy, qualitative research, hypogonadism

History

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Introduction

Classic male hypogonadism (i.e. testosterone deficiency) is the direct consequence of pathologies such as testicular failure or hypothalamic-pituitary dysfunction. Testosterone replacement therapy (TRT) is a therapeutic option generally recommended for men with classic hypogonadism, with the goal of restoring testosterone levels to the ''normal'' male physiological range [1]. Age-related declines in testosterone (referred to as age-related hypogonadism or late-onset hypogonadism ''LOH'') may also be treated with TRT. However, LOH is not well understood, and the medicalization of this condition as ''low-T'' or ''andropause'' has garnered considerable controversy [2,3].

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There is mixed evidence on the efficacy and safety of TRT in older men [4–7]; a recent systematic review of 39 randomized control trials found no significant benefits from its use and limited data on harms [8]. The U.S. Food and Drug Administration has cautioned against TRT use for LOH [9], although other regulatory agencies (e.g. European Medicines Agency) have not done so [10]. Recent studies have highlighted a rise in the number of TRT prescriptions dispensed to both older *and* younger men in Canada and the USA [9,11–13], which elucidates a pattern of increasing TRT use among adult males in general. In the absence of clear evidence on the balance of harms and benefits, it is unclear how physicians in Canada decide to prescribe TRT for LOH. To date, there have been no published studies that have attempted to explain the trends of TRT prescription and use in Canada. Given that there could be safety concerns regarding TRT (e.g. risk of cardiovascular death) [14–17], more information is needed to understand the context surrounding recent reports of rising prescription and use of TRT, particularly related to LOH and other potential causes of

low testosterone that are not related to underlying diseases among adult males.

The purpose of this study is to explore factors that influence the prescription and use of TRT in Ontario, with a primary focus on TRT for LOH. The scope of the study does not include the investigation of influences on non-prescription TRT (e.g. TRT purchased by patients on the Internet for non-medical use). This work was conducted as part of a larger drug class review by the Ontario Drug Policy Research Network (ODPRN), which includes four complementary studies describing the cost effectiveness, safety, efficacy and utilization patterns of prescription TRT with the goal of providing rapid research findings to policy makers in Ontario's public drug funding program [18–21].

Methods

Study design

We conducted a qualitative study using the framework approach [22], a methodology that enables rapid and focused data collection and analysis by identifying *a priori* concepts from the literature [22,23]. Qualitative research can elucidate key perspectives on drug therapies and shed light on the subjective experience of patients and prescribers that is often excluded from quantitative research [24].

Sampling

We used purposive sampling to recruit three groups from Ontario: (1) male TRT users; (2) primary care clinicians (i.e. nurses, pharmacists, primary care physicians) and (3) specialists (i.e. physicians specializing in endocrinology or urology). In keeping with current practice in qualitative health literature, sampling continued until theoretical saturation – the point when little or no new findings were being gleaned from consecutive interviews [25]. Though this study had a primary focus on TRT use for LOH, our secondary focus was on examining factors related TRT use in general that may explain the overall rising trend in prescribing. Therefore we included adult men over the age of 18 using TRT for LOH, to treat classic hypogonadism, or for non-specific use. We also purposively sampled negative cases. Since most sampling methods in qualitative research are non-probabilistic there is an inherent risk of selection bias. To mitigate this, negative case sampling is used to select 1–2 participants from the study population who differ from the recruited sample so as to introduce diverse perspectives. A negative case is usually defined during the data collection period and is recruited as needed [26]; in this study, it was defined as a male patient who uses non-prescription TRT.

Our recruitment methods included distributing messages through fax, e-mail or social media; leveraging clinician networks and circles of contact and posting flyers in clinics. Recruitment continued until we achieved saturation of themes [27].

Data collection

We collected data through one-on-one, semi-structured, 30–60-min telephone interviews. The interview guide was informed by a literature scan and input from specialist clinicians. The guide, attached in Appendix A of Supplementary material, was influenced by concepts from the Triple-A Framework by Morgan et al. [28], which includes three key domains for pharmaceutical investigations: affordability, accessibility and appropriateness. Interviews were audio recorded and transcribed.

Data analysis

We analyzed data using the framework approach. A coding framework was developed to include topics from the raw data as well as *a priori* concepts. Two analysts independently coded data and discrepancies were resolved in consensus meetings. The framework was adapted during the coding process to include emergent ideas or themes.

Ethics approval

This study received research ethics approval in April 2014 from the St. Michael's Hospital Research Ethics Office.

Findings

Participant demographics

Twenty-two participants from across Ontario completed semi-structured interviews in this study including: nine patients (including one negative case), six primary care clinicians and seven specialists. Participant demographics can be found in Tables 1 and 2.

The themes below describe factors that participants perceived influence TRT prescriptions in adult men under two main headings – provider factors (diagnostic ambiguity and beliefs about appropriateness) and patient factors (access to information and drug seeking behavior). ''Providers'' refer to all types of clinicians that prescribe TRT, and ''patients'' refer to men who use TRT.

Provider factors

Diagnostic ambiguity

The non-specificity of LOH symptoms introduces a high level of uncertainty in the diagnosis of hypogonadism and subsequent prescription of TRT; in contrast, patients with classic

Table 1. Provider characteristics and demographics.

Total sample ($n = 13$)	*n*	%
Primary care clinicians		
Primary care physicians	3	23
Nurses	2	15
Pharmacists	1	9
Specialists		
Urologists	5	38
Endocrinologists	2	15
Years of practice		
<5	2	15
5–15	5	38
>15	6	47
Type of practice		
Full-time	12	91
Part-time	1	9
Geographic location		
Urban	13	100

hypogonadism were described as easier to diagnose than those with LOH. As such, various diagnostic strategies for LOH have been used, observed or experienced by participants (Table 3). Some providers expressed a desire to rule out other health conditions before starting a trial of TRT (Strategies A and B). Others preferred to start a patient on TRT first and monitor its effects before deciding if testing for other conditions is warranted. Both patient and provider participants mentioned that they know of primary care physicians or specialists who prescribe TRT without testing for low testosterone levels and based on informal discussions or email communication (Strategy F).

Providers who require testosterone testing prior to prescribing TRT explained that there is no consensus on what constitutes ''low'' or ''normal'' test results. Clinical guidelines on interpreting and administering diagnostic tests were perceived to be vague. Furthermore, since patients with low testosterone may be asymptomatic, some provider participants wondered whether cutoffs for normal ranges of serum testosterone should vary by individual.

> Is your current testosterone too low for you? or is it too low for what you are used to?— – Primary Care Physician

Providers described using total serum testosterone thresholds for hypogonadism that ranged from 0 to 15 nanomoles per liter. Providers and patients also described varying preferences for the types of tests used (i.e. total serum testosterone levels versus bioavailable testosterone levels). Some provider participants prefer the total serum testosterone test because it is covered by the Ontario Health Insurance Plan and because they doubt the accuracy of bioavailable tests conducted in private laboratories (Table 3, strategies A and D). Others conduct both tests and compare results (Table 3, strategies B and C). All specialist participants preferred to test patients in the morning and repeat tests at least twice, in accordance with clinical guidelines, whereas most patients and primary care clinician participants did not perceive the timing of the test or repeat testing as crucial for diagnosis.

Beliefs about appropriateness of TRT

Participants revealed three different perspectives on the appropriateness of TRT. First, some providers described it as a treatment that should be reserved only for ''profoundly low'' cases where men have lost the ability to produce testosterone due to disability, treatments or diseases. In general, specialist participants with an interest in pituitary disorders or oncology tended to hold this view. The second perspective came from primary care physician and specialist participants with an interest in men's health. This group tended to believe that appropriateness of TRT can vary depending on the individual patient's symptoms, test results and overall health profile. Physicians in this group were more likely to consider prescribing TRT to patients whose lab tests suggest that their serum testosterone levels are on the low end of normal. The last perspective came from primary care physician and general urologist participants who described that TRT may be appropriate for any patient with symptoms and a low test result, without consideration of the underlying causes of hypogonadism.

Table 2. Patient characteristics and demographics.

Total sample (n=9)	n	%
Age		
25–34	1	11
35–44	1	11
45–54	2	22
55–64	1	11
65+	4	45
Employment status		
Full-time	5	55
Part-time	0	0
Unemployed (retired, disability)	4	45
Type of hypogonadism (*related condition*)		
Classic (*Klinefelter's Syndrome*)	1	11
Classic (*HIV*)	1	11
Classic (*Hodgkin's Lymphoma*)	1	11
LOH	6	67
Years on TRT		
<5	6	67
5–15	2	22
>15	1	11
TRT prescribed by		
Family doctor	5	55
Urologist	2	22
Endocrinologist	1	11
Independent supplier	1	11
TRT currently using		
Delatestryl	3	33
Androgel	4	45
Andriol	2	22

Table 3. Diagnostic strategies described by both patient and provider participants.

Diagnostic Strategies Described by Participants*	Administration of a symptom questionnaire	Informal discussion about symptoms	Bioavailable/free testosterone test	Serum/total testosterone test	Testing to rule out other conditions (thyroid abnormalities, depression, etc.)
Strategy A	√	√		√	√
Strategy B		√	√	√	√
Strategy C		√	√	√	
Strategy D		√		√	
Strategy E		√	√		
Strategy F		√			

*Since these were qualitative interviews, we did not survey the number of participants who used each strategy, but included in the table those that were mentioned by physicians during discussion. The purpose of this table is to display the variety of diagnostic strategies that are potentially being used in Ontario; this list may not be entirely inclusive of all available strategies.

Provider discussions about appropriateness were also influenced by their interpretation of the limited evidence on the safety of TRT. Some believe that ''myths'' about the safety of TRT exist, specifically regarding the potential harms of TRT use in men with prostate cancer, but that the balance of evidence favors TRT. Others were more cautious because there are no studies on the long-term consequences of TRT in older men. The case of female hormone replacement therapy was cited as an example of an aggressively promoted treatment that ultimately resulted in notable harms.

> I can see how someone might see the latest studies and say, ''my God, this is proof that [TRT] are dangerous.'' Someone like me, who follows the literature, closer understands the potential risks and potential benefits. – Endocrinologist

Patient factors

Access to information

> A couple [of] months ago, [I was] having some blood work done and read an article in Esquire magazine about testosterone. I asked my family doctor to have that checked. – Patient

Participants described that patient access to information on TRT can facilitate their eventual TRT use. Provider participants noticed an increase in publicly available information on TRT, particularly the concept of ''andropause,'' which has been compared to menopause by pharmaceutical advertisers. Some provider participants felt that there was insufficient evidence to make this claim. Others who believe in andropause mentioned that they have posted advertisements in their clinic about TRT. Half of the patient participants described discovering TRT and learning about its effects through posters at their pharmacy or physician's office, through friends or coworkers, popular magazines or through Internet browsing. This initial discovery was often the gateway to targeted searching for more information on the benefits of TRT and how to access these drugs. Patients of all ages described how the information they read really ''*spoke to*'' their perceived needs, some of whom felt they had been misdiagnosed as having depression. Information on improved sexual function and energy levels was of particular interest to these participants.

The second half of patient participants described hearing about TRT for the first time through a suggestion from their physician, usually during a visit about a related condition (e.g. chemotherapy treatment). While most patient participants found it easy to access information on the positive effects of TRT and how to acquire it, they seemed to have little knowledge about its side effects or risks. Some expressed a desire to receive more information from their physician on the availability of different formulations, the pros and cons of each, as well as the risks of long-term use of TRT.

Drug seeking behavior

All participant groups discussed the persistence of some patients in attempting to acquire and use TRT. Provider participants described an increase in the number of patients requesting to be put on a trial of TRT. Some patients described spending hours thinking of ways to acquire TRT, talking to friends who use it and requesting referrals to specialists. One participant did not feel satisfied with his physician's advice, so he increased his TRT dose and subsequently requested switching products when he did not perceive any immediate effects. Another participant, who was recruited as a negative case for this study, described his experience of buying a topical TRT from a supplier at his gym. Patients who are particularly persistent have described going to multiple physicians until they were able to find one that was amenable to prescribing them TRT.

Discussion

This study provides insight on the rise in TRT prescription rates in Ontario, which may be relevant for other locales with similar trends. In the absence of consistent guidelines for LOH and long-term outcome studies on TRT clinicians may rely more heavily on beliefs and clinical judgment when deciding how to prescribe TRT to their patients. In this environment of uncertainty, patients who are persistent in their quest for TRT may be successful in either finding a physician who is willing to prescribing TRT or convincing their current physician to explore treatment options. The large volume of information available on TRT and its benefits may also be influencing more patients to request TRT trials. While our sample included both LOH and classic hypogonadism patients, similar themes were elucidated from both groups. The latter group was more likely to have heard about TRT from their physician.

To our knowledge, there are no other published studies that have specifically explored provider and patient perceptions of TRT prescription and use. International literature on hypogonadism and andropause has detailed various schools of thought on diagnosis or treatment and points to a need for more research [29–34]. A 2006 survey revealed that 70% of primary care physician respondents in Victoria, BC were treating male patients with TRT, although 57.4% of respondents shared hesitations with LOH diagnosis such as: (a) a personal belief that andropause is not a clinical condition and (b) a lack of appropriate educational resources to diagnose or manage it [35]. A 2007 study revealed that 52.7% of Manitoban men prescribed TRT never had a testosterone test [36]. Our study expands on these findings by describing how diagnostic ambiguity and physician beliefs about appropriateness can influence these TRT prescribing patterns.

Though various guidelines exist and are clearer for diagnosing classic hypogonadism, they lack the specificity needed to diagnose LOH. One issue is that the definition of ''low'' serum testosterone level (i.e. nmol/L of serum testosterone) is not standardized across guidelines [1,37–40], with suggested indicators for deficiency ranging from 6.9 to 11 nmol/L. The European Association of Urology's Guideline has acknowledged that hypogonadism is ''*more subtle and not always evident by low testosterone levels.*'' The American Endocrine Society's expert panelists had varying opinions about indicators, with their conclusion

being that the ''*lack of definitive studies precludes an unequivocal recommendation*'' for older men with lower testosterone levels. Our research elucidates the need for clear, systematic and standardized guidelines on the diagnosis of LOH. Widespread dissemination of these guidelines to raise awareness of TRT prescribing recommendations among primary care and specialist physicians is warranted.

Our findings demonstrate how patient access to information on TRT and patient motivation may influence TRT use in men with varying causes of hypogonadism. Other studies have confirmed that common sources of non-clinical information for prospective patients are: the Internet, popular press and mass media [41,42]. Online resources claiming that testosterone deficiency is common, especially for older men, are hosted by drug manufacturers and are key sources of publicly available information [43,44]. This may cause men with non-specific symptoms to buy-in to the belief that they have testosterone deficiency, and that TRT may increase their quality of life [43,45]. Our findings indicate that patients may be less aware of the potential risks of TRT, which highlights a need to provide more comprehensive information outlining both risks and benefits to patients who are inquiring about TRT in clinical settings.

Limitations

We aimed to include as many diverse viewpoints as possible, given the time constraints of our rapid qualitative inquiry; however, patient participant recruitment was the primary limitation of our study. Currently, there is no consensus regarding what should be an appropriate sample size for qualitative studies [46]. Since the patient group was a less homogeneous group in comparison with the clinician groups, we were hoping for a slightly larger sample of patients [25,27]. Other researchers have reported difficulty in recruiting men for TRT research [47]; potential reasons for this may be the sensitive nature of the health topics surrounding TRT (e.g. libido). Despite this challenge, saturation of themes was achieved in all participant groups. Therefore, we posit that a larger sample of patients may not have yielded more meaningful results.

The second limitation of this study is that, due to the small sample size, the findings may not be representative of the general population from which our study sample was drawn. It should be noted that this limitation is an inherent feature of qualitative research. The goal of qualitative research is generally to obtain detailed descriptions of experiences and perceptions in an effort to explain phenomena – it does not attempt to describe variation across a population, as in quantitative research [25].

Conclusion

This study provides context for patient and provider decision-making as it relates to utilization trends of TRT in Ontario. The findings highlight that much work still needs to be done to improve diagnostic accuracy and encourage appropriate TRT prescription. In addition, both patients and providers need more information about the risks and long-term effects of TRT.

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Declaration of interest

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Supplementary material available online