

Sex and gender considerations in Canadian clinical practice guidelines: a systematic review

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Abstract

Background: The importance of sex and gender in the diagnosis and management of health conditions is well established, but the extent to which this evidence is integrated into clinical practice guidelines remains unknown. We aimed to determine the proportion of Canadian clinical practice guidelines that integrate evidence on sex and gender considerations.

Methods: We searched the Canadian Medical Association's CPG Infobase, PubMed, all provincial/territorial websites and websites of professional organizations for English- and French-language Canadian clinical practice guidelines published between January 2013 and June 2015 on selected conditions identified as priorities by policy-makers and practitioners. Citations and text were searched electronically using keyword terms related to sex and gender. Three investigators independently analyzed and categorized the content of text-positive clinical practice guidelines based on clinical relevance for practitioners.

Results: Of the 118 clinical practice guidelines that met the inclusion criteria, 79 (66.9%) were text-positive for sex and/or gender keywords; 8 (10%) of the 79 used the keywords only in relation to pregnancy. Of the remaining 71 guidelines, 25 (35%) contained sex-related diagnostic or management recommendations. An additional 5 (7%) contained recommendations for sex-specific laboratory reference values, 29 (41%) referred to differences in epidemiologic features or risk factors only, and 12 (17%) contained nonrelevant mentions of search keywords. Twenty-five (35%) of the text-positive guidelines used the terms "sex" and/or "gender" correctly.

Interpretation: Recommendations related to sex and gender are inconsistently reported in Canadian clinical practice guidelines. Guidelines such as the Sex and Gender Equity in Research guidelines may help inform the meaningful inclusion of sex and gender evidence in the development of clinical practice guidelines.

Manifestations and outcomes of disease, including cardiovascular conditions,¹⁻⁴ immune disease,^{5,6} respiratory illness⁶⁻⁸ and mental health conditions,^{9,10} have long been known to differ between men and women. These differences relate to sex (molecular, cellular and epigenetic mechanisms of male and female physiology) and gender (adopted or imposed social norms, behaviours, identities and expectations).^{11,12} Better understanding of these mechanisms has led to a near-linear rise in sex- and gender-specific research publications since the 1990s in all medical disciplines,¹³ although terminology can be confused.¹¹

Despite new evidence on differences between males and females, the uptake of sex and gender influences into clinical practice guidelines and clinical practice has been slow.¹⁴ The development of clinical practice guidelines is a critical first step for translating research findings into clinical practice to narrow the "know-do" gap^{15,16} and improve patient care. The consequences of not including evidence about females and

males separately in clinical practice guidelines can range from missed opportunities to prevent type 2 diabetes in fathers of children whose mothers had gestational diabetes¹⁷ to inappropriate prescription of certain cardiovascular drugs to women based on altered risk-benefit profiles.¹⁸ For example, in 2014, Health Canada issued a warning to cut the recommended dosage of zolpidem, a common sleeping pill, for women by half because morning blood levels of the drug are

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higher in women than in men, with increased risk of driving impairment.¹⁹ Rochon and colleagues²⁰ discovered that, in Ontario, men with dementia who were prescribed antipsychotic drugs had significantly higher risks for hospital admission and death than did women with dementia. Similarly, social risk factors are associated with higher rates of suicide in older men, which suggests that more aggressive screening and treatment may be required.^{21–23}

The extent to which evidence about sex and gender is integrated into clinical practice guidelines for diagnosis and management of diseases remains unknown. We conducted a systematic review to investigate the integration of sex and gender evidence into Canadian clinical practice guidelines published between 2013 and 2015 for noncommunicable health conditions.

Methods

Data sources and inclusion criteria

Protocols for this review are posted on Open Science Framework and follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines (www.prisma-statement.org/). The review search focused on selected health conditions identified as priorities by policy-makers and practitioners^{24–30} (Box 1). We considered only 2 cancers, lung and colorectal, because they are among the leading causes of death from cancer for both females and males,³¹ and important sex and/or gender differences in prev-

Box 1: Health conditions identified as priorities by policy-makers and practitioners^{24–30} and included in the search for clinical practical guidelines

Acute coronary syndrome	Fibromyalgia
Addictions	Generalized anxiety disorder
Alcohol drinking	Heart failure
Angina pectoris	Hypertension
Anxiety disorders	Insomnia
Asthma	Mental health conditions
Atrial fibrillation	Migraine
Back pain	Myocardial ischemia
Cancer, colorectal	Neuralgia
Cancer, general	Obesity
Cancer, lung	Osteoarthritis
Cardiomyopathies	Pain
Cardiovascular diseases	Peripheral vascular diseases
Chronic obstructive pulmonary disease	Polyps
Coronary artery disease	Pulmonary embolism
Dementia	Pulmonary hypertension
Depression	Stroke
Diabetes	Substance dependence
Diabetic nephropathies	Thrombosis
Dyslipidemias	Transient ischemic attacks
Emphysema	Venous thromboembolism

alence, risk and screening, pathophysiologic characteristics, diagnosis, treatment and outcomes for these conditions have been found.^{32–36}

We searched the Canadian Medical Association's database (CPG Infobase) of about 1200 clinical practice guidelines developed or endorsed by authoritative medical or health organizations in Canada³⁷ for guidelines related to the identified health conditions. We also searched PubMed, all Canadian provincial/territorial websites and professional association websites for English- and French-language clinical practice guidelines using the search term "clinical practice guideline." Only documents published in Canada between January 2013 and June 15, 2015 were included. We chose these dates because Health Canada's Health Portfolio Sex and Gender-Based Analysis Policy³⁸ was issued in 2009; new research under the policy would be published 1 to 2 years later, and at least 2 more years are required to review evidence and develop a clinical practice guideline.¹⁶ We excluded original research, reviews, opinion pieces and editorials as well as clinical practice guidelines for single-sex health conditions such as menopause and prostate or gynecologic cancers. Duplicates were removed.

Data extraction and quality assessment

We searched the text and citations of clinical practice guidelines electronically for the keywords "sex," "gender," "male," "female," "men," "women," "man," "woman," "boy," "girl" and "pregnan*." We searched for clinical practice guidelines in French using the keywords "sexe," "genre," "sexo-spécifique," "homme," "hommes," "femme," "femmes," "fille," "filles," "garçon," "garçons" and "grossesse." We did not perform risk-of-bias assessments, as there is no validated strategy for sex and gender integration in clinical practice guidelines. Guidelines were considered text-positive if they had any keywords in the main text and text-negative if they had no keywords in the main text.

Data synthesis and analysis

We assigned guidelines that covered more than 1 health condition to the condition most emphasized in the text. Text-positive and text-negative guidelines were treated separately. Three investigators (C.T., B.C. and M.H.-B.) independently analyzed the content of every text-positive guideline for the type, amount and applicability of evidence presented on epidemiologic features, risk and screening, pathophysiologic characteristics, symptoms and diagnosis, and treatment/interventions.¹⁴

We assigned text-positive guidelines to 1 of 5 categories according to the relevance of the information to clinical practice. Guidelines were assigned to category 1 if evidence-informed recommendations were made that supported different approaches for men and women, and to category 2 if the evidence presented supported the use of a singular approach for women and men. Category 3 included guidelines with sex-specific reference values for laboratory data. Guidelines that reported sex or gender differences in epidemiologic features or risk factors but did not make suggestions for clinical management were assigned to category 4. Category 5 was reserved for

guidelines that made only superficial mention of 1 or more of the search terms. The use of “sex” and “gender” specifically was assessed for adherence to current definitions.^{11,38} Differences in categorization were resolved by consensus.

Outcomes

The primary outcome of the review was the proportion of clinical practice guidelines that mentioned sex or gender or both, defined as the number of guidelines that were text-positive for any keyword over the total number of guidelines included in the review. Secondary outcomes were a qualitative analysis³⁹ of whether the inclusion of evidence in the text was clinically relevant, and the appropriate use of the terms “sex” and “gender” according to the Sex and Gender Equity in Research guidelines.¹¹

Statistical analysis

We did not conduct statistical analyses of guideline data as the intent of this review was strictly to identify and categorize any mentions of sex- or gender-related words in the clinical practice guideline texts.

Results

The search identified 347 Canadian clinical practice guidelines that addressed 1 or more of the health conditions under consideration. We excluded 229 guidelines because of publication before 2013, a sex-specific topic or duplication, yielding 118 guidelines for final inclusion in the analysis (Figure 1), 3 of which were in French only.

Inclusion of sex and/or gender information

Of the 118 clinical practice guidelines, 79 (66.9%) were text-positive for sex and gender keywords. Eight of the 79 (10%) used keywords only in relation to pregnancy. Of the 71 remaining guidelines, 25 (35%) contained sex-related diagnostic or management recommendations; 21 (30%) recommended different approaches for men and women, and 4 (6%) recommended similar approaches based on evidence (categories 1 and 2, respectively). Five guidelines (7%) included recommendations for sex-specific laboratory reference values (category 3). Twenty-nine guidelines (41%) referred to differences in epidemiologic features or risk factors only (category 4), and 12 (17%) contained mentions not relevant to clinical practice (category 5).

Of the 39 text-negative guidelines, 5 (13%) contained citations in the reference lists alluding to the presence of sex differences in the condition of interest. For example, a guideline on the pharmacological management of chronic neuropathic pain contained no keywords in the body of the text but cited 2 articles on the effects of sustained-action opioids on women and men.⁴⁰

Type of sex and gender evidence cited in text-positive clinical practice guidelines

The nature of sex-specific information reported in text-positive clinical practice guidelines varied (Table 1). For

example, 1 guideline stated that “colorectal cancer is the third most common cancer ... in both sexes,”⁶⁸ whereas a few provided sex-disaggregated risk and mortality data, such as “The probability of developing colorectal cancer increases with age and varies with sex ... i.e., 1/32 males and 1/36 females will die of invasive colorectal cancer.”^{69,70}

Other guidelines mentioned sex as a risk factor but only in absolute terms, such as noting that female sex is a risk factor for depression in patients with diabetes⁷¹ or that female adolescents with type 1 diabetes are at risk for eating disorders.⁷² Sometimes the comparative risk of different outcomes in men and women was mentioned in broad terms, such as following stroke, when women are at greater risk for depression whereas men are at greater risk for vascular dementia.⁷³ In rare instances, sex differences in risk were explicit: “Estimates of risk of ischemic stroke in people with diabetes range from a 2- to 3-fold increase in men and a 2- to 5-fold increase in women.”⁷⁴ In only 2 cases were gender differences noted, as in the case of perceptions and interpretations of pain.⁶⁷

Some guidelines provided evidence that can inform clinical practice. For example, guidelines on alcohol consumption recommended a lower diagnostic screening threshold for risky drinking behaviour for women than for men,^{53,54,75} although only 1 guideline explained biological differences in alcohol absorption rates by sex.⁵³ Another guideline suggested that women respond more favourably than men to outpatient care.⁷⁵ Two guidelines alluded to hormonal causal pathways for aggravated hypertension in women, highlighting modifiable treatment strategies in the form of discontinuation of oral contraceptive and exogenous sex hormone therapies.^{45,76} A recommendation to avoid antidepressants with strong cytochrome P450 2D6 inhibition (e.g., paroxetine, fluoxetine) in premenopausal survivors of breast cancer requiring tamoxifen therapy can be applied in practice.⁷⁷ As well, a guideline on heart failure in children and youth warned that treatment with spironolactone can lead to irreversible gynecomastia in males, affecting long-term psychological outcomes.⁷⁸

Conversely, some guidelines did not address the clinical implications of sex and gender differences. A guideline noting differences in response to medication between male and female children and adolescents with type 2 diabetes did not recommend distinct treatment choices.⁷² Similarly, guidelines that described a higher rate of adverse effects of statin use in women than in men did not offer assistance for selecting alternative therapies to lower lipids.^{59,79,80}

Uses of “sex” and “gender” evidence in clinical practice guidelines

Text-positive clinical practice guidelines also varied in the correct use of the terms “sex” and “gender.” Of the 79 guidelines, 37 (47%) did not use either term explicitly, 14 (18%) used one or the other, but not according to the accepted definitions, and 25 (32%) used at least 1 term appropriately. One guideline (1%) used “sex” in the context of sexual activity only.

Interpretation

We found inconsistencies in the extent and degree to which evidence on sex and gender is incorporated into Canadian clinical practice guidelines. Only 35% of guidelines reported screening, diagnosis or management considerations specific to sex or gender, and only 25% used the terms “sex” and “gender” correctly. Given early recognition of sex and gender differences in mental health conditions

and cardiovascular disease, we expected clinical practice guidelines in these fields to reliably highlight information about females and males separately.¹³ Recent attention to sex differences in cancer,^{81–83} lung disease^{6–8} and diabetes^{84–86} predicted meaningful uptake in these areas as well. Although some clinical practice guidelines targeting these conditions incorporated differentiated data in a way that guides practice, many keyword mentions were superficial and of limited value.

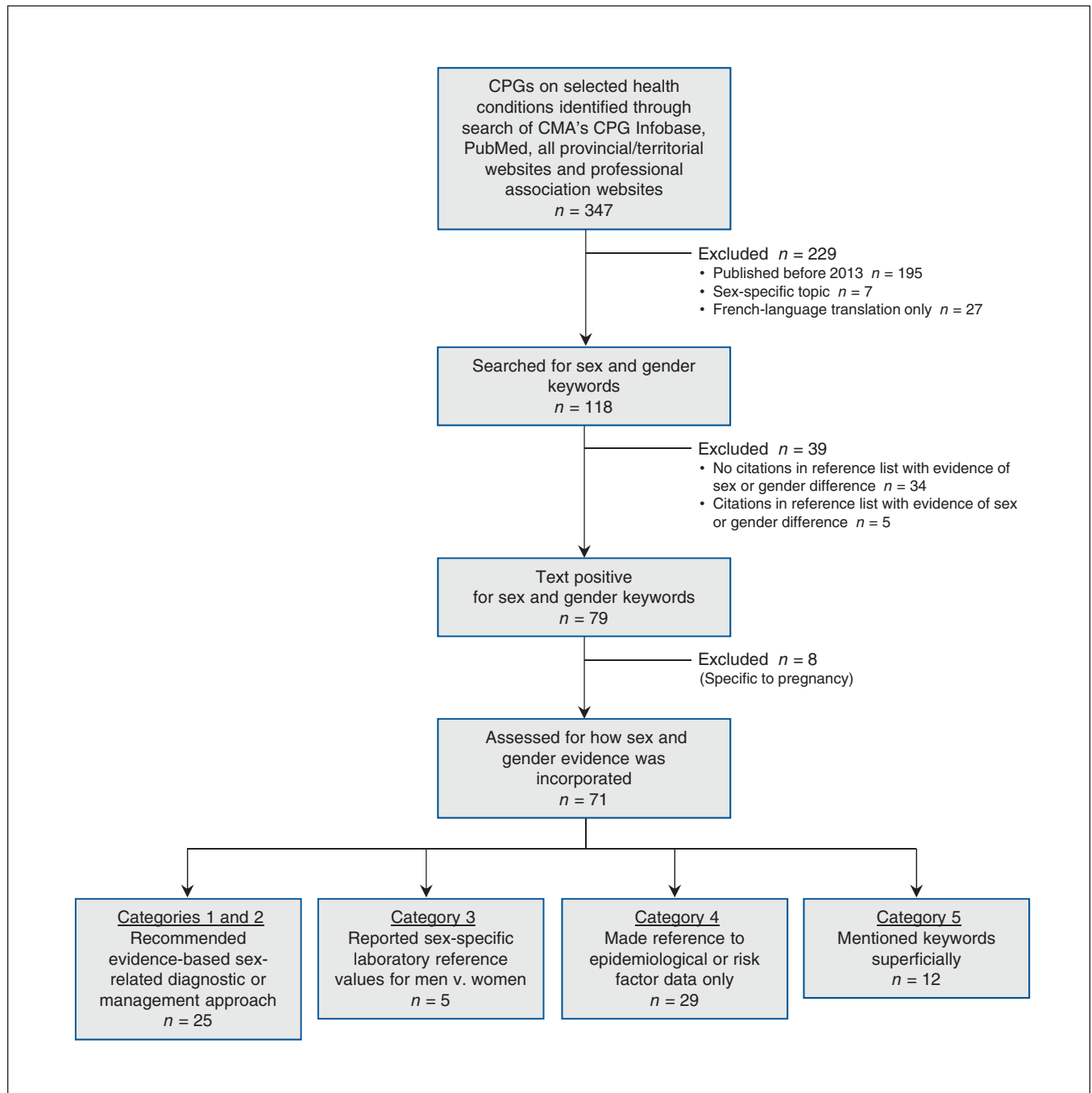


Figure 1: Flowchart showing the inclusion and exclusion criteria that were applied to the initial sample of 347 Canadian clinical practice guidelines on selected health conditions. A total of 71 text-positive guidelines were categorized as a function of the clinical relevance of the information provided. CMA = Canadian Medical Association, CPG = clinical practice guideline.

Table 1: Examples of sex- and gender-related information included in various clinical practice guidelines

Condition	Quote from guideline	Group
Guideline specifically recommends evidence-based diagnostic or management approach for men/women or boys/girls		
Ischemic heart disease	Noninvasive testing not normally recommended for women < 60 years of age or men < 40 years of age with only 1 classical risk factor for angina	Canadian Cardiovascular Society ⁴¹
Stroke	Acetylsalicylic acid recommended for reducing the risk of stroke in women only. Stroke unit care is equally beneficial for men and women.	Canadian Stroke Best Practices and Standards Working Group ⁴²
Diabetes	Acetylsalicylic acid recommended for reducing nonfatal myocardial infarction in men but not women without a history of cardiovascular disease	Canadian Diabetes Association Clinical Practice Guidelines Expert Committee ⁴³
Childhood diabetes	Adolescent females with type 1 diabetes should be regularly screened for eating disorders using nonjudgmental questions about weight and body image	Canadian Diabetes Association Clinical Practice Guidelines Expert Committee ⁴⁴
Hypertension	Recommended target of a healthy body weight (body mass index 18.5–24.9 kg/m ² , with a waist circumference < 102 cm for men and < 88 cm for women)	Canadian Hypertension Education Program, ^{45–48} Canadian Diabetes Association Clinical Practice Guidelines Expert Committee ⁴⁹
Dyslipidemia	Recommend plasma lipid screening in men > 40 years for low high-density lipoprotein (< 1.0 mmol/L) and in women > 50 years for low high-density lipoprotein (< 1.3 mmol/L)	Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, ⁵⁰ Canadian Cardiovascular Harmonized National Guidelines Endeavour ⁵¹
Primary prevention of childhood obesity	Educational interventions with a social learning foundation may be more effective with girls, while interventions that change environment to enable physical activity may be more effective with boys	Registered Nurses' Association of Ontario ⁵²
Low risk drinking guidelines	Screen for at-risk drinking in men < 65 years: 5 or more drinks on 1 or more days in the last year. Limit to no more than 3 drinks in any day, 15 per week. Screen women < 65 years for 4 or more drinks on 1 or more days in the last year. Limit to no more than 2 drinks in any day, 10 per week.	Collège des médecins du Québec/ Éduc'alcool, ⁵³ British Columbia Ministry of Health ^{54,55}
Guideline acknowledges different laboratory reference values for men/women or boys/girls		
Heart failure	Recommends using World Health Organization definition of anemia: hemoglobin concentration < 130 g/dL for men and < 120 g/dL for women	Canadian Cardiovascular Society ⁵⁶
Diabetic nephropathy	4-variable Modification of Diet in Renal Disease equation requires knowledge of the patient's sex for laboratory calculation of the estimated glomerular filtration rate	Canadian Diabetes Association Clinical Practice Guidelines Expert Committee ⁵⁷
Asthma	Spirometry reference values determined by sex	Canadian Thoracic Society ⁵⁸
Guideline mentions epidemiologic or risk factor data only, without recommendations		
Dyslipidemia	Women > 80 years are at increased risk for statin-induced myopathy	Canadian Diabetes Association Clinical Practice Guidelines Expert Committee ⁵⁹
Heart failure	Female patients are more likely to have nonischemic cardiomyopathy. Making a diagnosis of heart failure in women is considered to be more difficult, because the cardinal triad of edema, fatigue and dyspnea are neither sensitive nor specific manifestations and atypical presentations occur more frequently.	Canadian Cardiovascular Society ⁶⁰
Diabetes	Thiazolidinediones increase the risk of fracture in older women Aboriginal women in Canada have a 2 to 3 times higher rate of gestational diabetes than others	Canadian Diabetes Association Clinical Practice Guidelines Expert Committee ⁵⁰
Anxiety disorders	Women generally have higher prevalence rates for most anxiety disorders, compared to men	Canadian Anxiety Guidelines Initiative Group ⁶¹
Substance dependence	Gender identity and gender expression are risk factors for a substance use disorder owing to widespread marginalization and discrimination	Registered Nurses' Association of Ontario ⁶²
Colon cancer	The risk for development of colon cancer is higher in males than in females. Female sex is associated with more adverse events from colonoscopy, longer duration and incomplete examinations.	Cancer Care Ontario ^{63,64}
Guideline makes superficial reference to the keywords sex, gender, men/women or boys/girls		
Coronary artery disease	Only 28% of the patients in the trial were women	Canadian Cardiovascular Society Heart Failure Management Primary Panel ⁶⁵
Chronic obstructive pulmonary disease	Benefits of antibiotic administration on exacerbation rates were significant in 1 study, even after adjustment for sex	American College of Chest Physicians/ Canadian Thoracic Society ⁶⁶
Pain	Pain scale has 6 gender-neutral faces	Registered Nurses' Association of Ontario ⁶⁷

These findings are similar to those reported from the Netherlands, where a preliminary study showed that sex-related factors or effects were mentioned in only 20% of clinical practice guideline recommendations for osteoporosis and were completely absent in clinical practice guidelines on depression.⁸⁷

Several reasons may account for the variable inclusion of disaggregated evidence in clinical practice guidelines. A simple explanation is the lack of research on sex and gender differences in medicine. With most biomedical experiments conducted exclusively on male animals and substantial underrepresentation of women in clinical trials, it is possible that many sex and gender differences have yet to be discovered.^{88,89} Although more publications that consider females and males separately in medicine are emerging, less than 25% address differences in management decisions for patients based on sex or gender.¹³

Another explanation for the suboptimal integration of sex and gender considerations into clinical practice guidelines relates to the lag time between research discovery and practice transformation.^{90,91} A recent study showed that microglial cells play a role in mediating pain pathways in male mice, whereas T cells are responsible for this same function in female mice.⁹² It is not known when and how this information will translate into different analgesic drug targets for men and women. Pharmacoepidemiological findings and postmarketing drug safety warnings on the differential risks of adverse drug reactions in women and men do not seem to substantially change entrenched prescribing patterns.⁹³ Future clinical practice guidelines on insomnia should incorporate Health Canada's 2014 recommendation to cut the dosage of sleeping pills in half for women.¹⁹

Finally, failure to integrate such considerations into clinical practice guidelines likely results from lack of awareness as well as lack of guidance on how to do so.^{87,94,95} Current guideline development instruments do not provide instruction for synthesizing sex and gender evidence.⁹⁶ The AGREE (Appraisal of Guidelines, Research and Evaluation) II instrument requires systematic reviewers to specify populations of interest, but does not require identification of evidence particular to males or females or any note of sex or gender differences.⁹⁷ The same is true for GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines.⁹⁸⁻¹⁰⁰ Unless a clinical practice guideline working group specifically asks a question about evidence-based sex and gender differences, it is unlikely that the correct search terms will be used to query the literature.

Several instruments exist to guide the inclusion of sex and gender. The Health Equity Group at Cochrane Canada encourages systematic reviewers to consider sex, gender and other equity dimensions, providing user templates.¹⁰¹ The Sex and Gender Equity in Research guidelines provide rationales and guidance for clinical practice guideline reviewers to look for and incorporate evidence on sex differences and gender and to use the terms appropriately.^{11,102} Song and colleagues¹⁰³ published a validated search strategy for uncovering publications that report sex-specific diagnostic and treatment evi-

dence. Standardized application of these strategies could enhance the uptake of evidence that is sex and gender specific in future clinical practice guidelines.

Limitations

A strength of our systematic review is that we used Canadian, provincial and academic Web sources to search for clinical practice guidelines, and the search terms were broad and inclusive. One limitation is that our findings risk overestimating perceptions that sex and gender evidence is meaningfully integrated into Canadian clinical practice guidelines. Ultimately, only 25 (21.2%) of the 118 clinical practice guidelines included in our review provided relevant sex-related diagnostic or management recommendations. We did not perform risk-of-bias assessments of the quality of the guidelines. A systematic search for sex- and gender-specific evidence that was omitted from clinical practice guidelines would permit an assessment of any missed opportunities to appropriately include information about male and female patients in clinical practice guidelines.

Conclusion

Gender-responsive health care takes into account all sex- and gender-related factors for women and men. Practitioners are increasingly requiring male- and female-specific information. For example, specialists in heart failure have explicitly called for sex-specific diagnostic criteria and treatments. The implications of this systematic review on future clinical practice guideline development are twofold. First, we suggest that guidelines for developing clinical practice guidelines be revised to emphasize the importance of including subquestions and search strategies that reveal evidence on sex and gender differences in medicine. Second, we recommend that a focus on sex- and gender-responsive interventions be prioritized not only in clinical practice guidelines but also in medical school curricula and continuing education to consolidate Canadian innovation in personalized care.

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