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Mapping the Evidence: Sex Effects in High-impact Conditions for Women Veterans – Depression, Diabetes, and Chronic Pain

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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INTRODUCTION

The Veterans Health Administration (VHA) has prioritized systematic, evidence-based improvements in the delivery of healthcare to women Veterans. Women are entering the military at unprecedented rates. Women currently represent more than 20% of recruits, and women Veterans now number more than 2 million, accounting for nearly 8% of the U.S. Veteran population.[1,2] The number of women Veterans using VHA services has doubled in the past decade,[3] in part as a result of higher enrollment among Veterans returning from Iraq and Afghanistan.[2] During the 2012 fiscal year, 362,014 women Veterans sought medical care at VHA facilities, and compared with their male counterparts, they were younger, more ethnically diverse, and more likely to reside in urban areas.[3]

Women Veterans have distinct health problems and healthcare priorities compared with male Veterans. The burden of mental health disorders, such as depression, is higher for women Veterans compared with male Veterans.[4-6] More than one-fifth of women Veterans have been exposed to military sexual trauma,[7] and such exposures are associated with higher rates of posttraumatic stress disorder[8] and other chronic medical illnesses.[9] Musculoskeletal conditions are also highly prevalent, affecting 55.9% of women Veterans.[3]

While there has been increasing awareness of sex and gender differences in health and healthcare, particularly since national initiatives in the early 1990s to improve participation by women in clinical research,[10] there are still significant challenges in applying the clinical evidence base to women. For example, there was only 30% overall participation by women in clinical trials used to support the 2007 American Heart Association guidelines for cardiovascular health in women.[11] Additionally, published studies infrequently report or discuss the appropriateness of analyses for sex or gender effects.[12,13] This may be due in part to hesitation about discussing subgroup analyses from clinical trials that were underpowered to detect sex differences.[14,15] Also, when patients are randomized to treatment groups and subsequently divided according to sex, the latter division is not random.[16] The presence of such deficits in our clinical knowledge base is especially concerning given well-documented sex differences in effectiveness and adverse effects for some treatments, including certain medications.[17-19] Thus, systematic evaluation of current clinical evidence for sex differences in treatment effectiveness, along with identification of key gaps in our knowledge of these differences, is a critical next step for improving health outcomes for women Veterans.

The VHA's Women's Health Service (WHS) oversees national policy, clinical operations, and research programs that address the healthcare needs of women Veterans. The WHS requested an evidence map to aid prioritization and development of implementation projects and research initiatives. Evidence mapping is an emerging approach that describes key characteristics of existing studies for a broad area of medicine.[20-22] In this project, we used evidence mapping to (1) better understand sex differences in intervention outcomes for high-impact medical conditions, (2) identify effective interventions for women, and (3) identify gaps in evidence about the efficacy and effectiveness of interventions in women.

METHODS

Our aim was to deliver an evidence map that provides (1) an overview of the volume of studies evaluating interventions for selected high-impact conditions in women Veterans and (2) a set of executive summaries that describe the effects of these interventions and whether there has been evaluation of differential effectiveness in women compared with men (hereafter referred to collectively as "sex effects").

Consistent with the general principles of evidence mapping, our goal was to provide high-level information about broad questions rather than detailed information on a narrow set of questions. We used a stakeholder-driven approach to identify high-priority conditions and interventions. Given the diversity of interventions and range of prioritized conditions, we focused on systematic reviews in order to best estimate the volume of research and treatment effects. Systematic reviews follow a structured approach to identifying relevant studies and summarize the results, often using quantitative estimates (*ie*, meta-analyses) to generate pooled effect estimates. For treatment efficacy, we prioritized results from systematic reviews that exclusively used randomized trials for effect estimates. However, we did not conduct a quality assessment of these studies, and estimates of treatment effect should be interpreted cautiously. For adverse effects, we also closely examined systematic reviews that included observational studies. We piloted our methodology in an evidence map of a set of diverse interventions for depressive disorders and presented these results to key stakeholders. We then refined our methods and applied the updated protocols to the remaining conditions of interest.

TOPIC PRIORITIZATION

We used a forced-rank methodology that included presentation of initial rankings to stakeholders, followed by discussion and reranking to identify conditions for inclusion in the mapping project.[23] Stakeholders included representatives from HSR&D Center for the Study of Healthcare Innovation, Health Services Research and Development Service, Office of Research and Development, the Women's Health Research Network, Women's Health Services, and Mental Health Services, Department of Veterans Affairs. We initially selected 34 conditions based on (1) disease prevalence among U.S. women and women Veterans, (2) the burden of disease, (3) the availability and breadth of effective treatments, and (4) women Veterans' priorities for gender-specific care (Appendix A).[3,24-28] Given resource capacity, it was agreed with stakeholders that we would address a limited set of these conditions. We used multiple rounds of iterative prioritization to select the final conditions of interest. After the first round, depression and chronic pain were ranked highest, but 4 conditions (obesity, type 2 diabetes, posttraumatic stress disorder, and alcohol use disorder) had very similar prioritization scores. Thus, we submitted these 4 conditions to a second round of priority rating, and diabetes was rated highest priority in this group. We also focused the chronic pain topic to more specific diagnoses in order to better determine eligible interventions and improve interpretation of our results. Our final conditions of interest were the following: (1) depressive disorders, (2) type 2 diabetes, and (3) chronic pain (consisting of 3 diagnoses: chronic low back pain [CLBP], fibromyalgia [FM], and chronic knee pain due to osteoarthritis [knee OA]). For each condition, we selected treatments in broad categories, including medications, behavioral interventions, supervised exercise, and quality improvement interventions. We also included certain condition-

specific interventions, such as bariatric surgery for diabetes, and joint injections, acupuncture, and spinal manipulation for chronic back and knee pain (Table 1).

Table 1. Eligible interventions and outcomes for medical conditions of interest

	Depressive disorders	Type 2 diabetes	Chronic pain conditions
Interventions	· Antidepressants · Psychotherapy · Guided self-help · Exercise · Quality improvement[a]	· Insulin, oral medications · Psychoeducation, weight management · Exercise · Quality improvement[a] · Bariatric surgery	· Antidepressants, muscle relaxants, anticonvulsants · Psychotherapy, biofeedback, mindfulness-based practices · Guided self-help · Exercise · Acupuncture, spinal manipulation · Joint injections · Quality improvement[a]
Outcomes	· Symptom severity · Clinical response and remission · Functional status, quality of life · Adverse effects	· Glycemic control · Weight/body mass index · Microvascular and macrovascular events · Mortality · Adverse effects	· Pain severity · Fatigue[b] · Functional status, quality of life · Mortality · Adverse effects

[a] Quality improvement interventions included collaborative care, multidisciplinary care, and technology-enhanced interventions.
[b] Fatigue was an outcome only for fibromyalgia.

SEARCH STRATEGY

In collaboration with an expert reference librarian, we searched MEDLINE and the Cochrane Database of Systematic Reviews to identify eligible systematic reviews published from January 1, 2009, through October 31, 2014. Search strategies (Appendix B) used Medical Subject Headings (MeSH) and free-text terms for the conditions of interest, eligible interventions, and systematic reviews. We restricted the search to the past 6 years because systematic reviews are typically outdated within 5 years of publication and because of the likely high volume of relevant reviews.[29] In addition to electronic searching, we screened published reviews of reviews for eligible studies.

STUDY SELECTION

To be included in the evidence map, systematic reviews had to meet the following criteria:

- **Design:** Systematic reviews must describe a search strategy, eligibility criteria, and an analysis plan. We excluded clinical guidelines, systematic review protocols, and reviews focusing on a single drug unless the drug uniquely represented a class of medications (*eg*, metformin) or the review used individual patient data (IPD) meta-analysis. We prioritized IPD meta-analysis because these studies are well suited to evaluating moderator effects.[30]
- **Participants:** Systematic reviews must focus on adults with one of the eligible conditions (depressive disorders, diabetes, or chronic pain conditions). Reviews that evaluated

mixed conditions were included if they reported results separately for an eligible condition.

- **Interventions:** For each condition, we included interventions in several broad categories, including medications, behavioral interventions (*eg*, psychotherapy, psychoeducation), exercise performed in organized groups (*eg*, tai chi, pool therapy) or with behavioral support, self-management strategies, and quality improvement interventions (*eg*, multidisciplinary care, technology-enhanced interventions). Table 1 summarizes the eligible interventions, including some condition-specific ones. Detailed eligibility criteria are provided in Appendix C.
- **Outcomes:** For each condition, we focused on outcomes that would be the most relevant for clinical providers and patients, including patient-centered outcomes such as symptoms and health-related quality of life. Refer to Table 1 for a summary and Appendix C for details.
- **Timing:** Any intervention duration and length of follow-up were eligible.
- **Setting:** Studies conducted in outpatient settings were preferred, but we accepted those that were in mixed or unclear settings.
- **Other criteria:** Only English-language systematic reviews published since January 2009 were included. For reviews with multiple publications (*eg*, technical monograph and journal article) or updated reviews (*eg*, 2 Cochrane publications by the same group on the same topic), we included only the most recent report, prioritizing the journal article over the monograph.

Two reviewers screened citations for eligibility, and citations deemed potentially relevant by either reviewer were retained for full-text review. Full-text publications were evaluated for eligibility by 2 reviewers; disagreements were resolved through discussion or by a third reviewer.

We anticipated that some interventions for each condition would have few or no systematic reviews that addressed sex effects. To determine the feasibility of a systematic review evaluating sex effects, we selected certain high-interest interventions for further evaluation. For each intervention, we selected the largest recent systematic review and used the list of included primary trials as candidates for review. We then examined those primary trials that randomized at least 75 patients per treatment arm and determined whether they reported sex effects. We chose this sample size criterion in order to limit our evaluation to trials that had the potential to be adequately powered to detect interaction effects (intervention * sex).[31] For depressive disorders, we looked at quality improvement interventions or psychotherapy, whereas for diabetes, we focused on diet, physical activity, and culturally tailored psychoeducation. For CLBP, we selected behavioral interventions, and for chronic knee OA, exercise interventions.

DATA ABSTRACTION

For depressive disorders and chronic pain conditions, we evaluated all eligible systematic reviews. For diabetes, we evaluated all reviews of nonpharmacological interventions and applied an additional procedure to prioritize among the large number of eligible systematic reviews addressing medications (n=120).

To prioritize the diabetes medication articles for abstraction, we first selected all reviews that examined multiple classes of medications and reviews of single-drug classes when there were 6 or fewer reviews per class. For medication classes with more than 6 eligible reviews (*ie*, metformin, incretin mimetics, insulin, and thiazolidinediones), we selected reviews using the following criteria: evaluated an entire drug class (vs single drug studies), published most recently, published in a top-tier journal (*eg*, *Journal of the American Medical Association, Annals of Internal Medicine, British Medical Journal*), conducted by an organization known for high-quality reviews (*eg*, Cochrane Collaboration), or evaluated outcomes such as glycemic control, cardiovascular events, mortality, or adverse events. The remaining unselected but eligible reviews (n=58) underwent a text search for sex effects and were fully abstracted only if the text search was positive (n=13).

Data were abstracted into a customized DistillerSR database (Evidence Partners Inc., Manotick, ON, Canada) by one reviewer and over-read by a second reviewer. Disagreements were resolved by discussion or by obtaining a third reviewer's opinion when consensus could not be reached. Abstracted data included study design (*eg*, systematic review with or without meta-analysis, network meta-analysis, or IPD meta-analysis), conditions, interventions, outcomes, the number and design of primary studies, proportion of men and women in included studies, and whether sex effects were part of study aims, analysis plan, and/or results. For studies containing sex-specific results, we also abstracted the number of studies included in the sex analyses, method used for evaluating sex effects (*eg*, meta-regression, subgroup analyses by study design characteristics), and sex effects of the intervention.

QUALITY ASSESSMENT

A formal assessment of systematic review methodological rigor was beyond the scope of this project. However, to indicate reviews of higher quality, we recorded whether the review was conducted by the Cochrane Collaboration, the Agency for Healthcare Research and Quality's Evidence-based Practice Centers, or the VA Evidence-based Synthesis Program. These organizations are known for their expertise and high-quality systematic reviews. Further, to help readers interpret estimates of treatment effect, we included review authors' comments on study quality or the overall quality of the evidence, when this was available.

DATA SYNTHESIS

We used descriptive statistics for the amount and types of evidence for included interventions per condition of interest (Table 2). We generated heat maps and barplots to graphically portray the number of studies (using the review with the largest number of included studies) and number of reviews reporting sex effects for each condition–intervention dyad. We report intervention sex effects in detail, giving priority to reviews using IPD meta-analyses and those originating from organizations known for high-quality reviews.

The primary goals of this synthesis were to describe the volume of recent systematic reviews, including the number of studies contributing to these reviews, and the number of reviews reporting sex effects. A secondary goal was to give general estimates of treatment effect. For these overall treatment effects, we prioritized higher quality, more recent, and more inclusive systematic reviews. Because there were often multiple reviews addressing the same intervention, we examined reviews for consistency of findings. However, we remind readers that the reviews have not been assessed for quality, and so in some cases the estimates of intervention effect may be incorrect.

Table 2. Definitions of statistical approaches used in the included systematic reviews

Term	Definition
Cohen's d	An appropriate measure of effect size for the comparison between 2 means. Cohen's d may be interpreted as the following: small effect=0.2 to <0.5; medium effect=0.5 to <0.8; large effect=0.8 or above.
Effect estimate or effect size (ES)	Refers collectively or generally to different versions of the SMD.
Hazard ratio (HR)	The ratio of the hazards, or chance of events occurring in 2 groups, such as the intervention arm compared with the control arm.
Hedges' g	A variation of Cohen's d that corrects for biases due to small sample sizes.
Individual patient data meta-analysis (IPD)	A specific type of systematic review. Rather than extracting summary (aggregate) data from study publications or from investigators, the original research data are sought directly from the researchers responsible for each study. These data can then be reanalyzed centrally and combined in meta-analyses, if appropriate.
Mean difference (MD)	A summary statistic used in meta-analyses of continuous data when outcomes are measured using the same scale (*eg*, blood pressure in mmHg). In some cases, an MD will be "weighted" wherein the "weight" given to each study reflects how much influence each study has on the overall results of the meta-analysis, determined by the precision of its estimate of effect.
Odds ratio (OR)	A summary statistic used in meta-analyses for dichotomous outcomes, it is the ratio of the odds of an outcome in 2 groups (*eg*, the odds of the outcome in intervention patients compared with the odds of the outcome in control patients).
Risk ratio (RR)	A summary statistic used in meta-analyses for dichotomous outcomes. Also called "relative risk," it is the ratio of the risk of an outcome in 2 groups (*eg*, the risk of the outcome in intervention patients compared with the risk of the outcome in control patients).
Standardized mean difference (SMD)	A summary statistic used in meta-analyses when the studies all assess the same outcome but measure it in a variety of ways (*eg*, all studies measure depression but they use different psychometric scales). SMD is the mean difference in outcomes between groups, divided by the standard deviation of the outcome among participants.

PEER REVIEW

A draft of this report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses are provided in Appendix D.

RESULTS

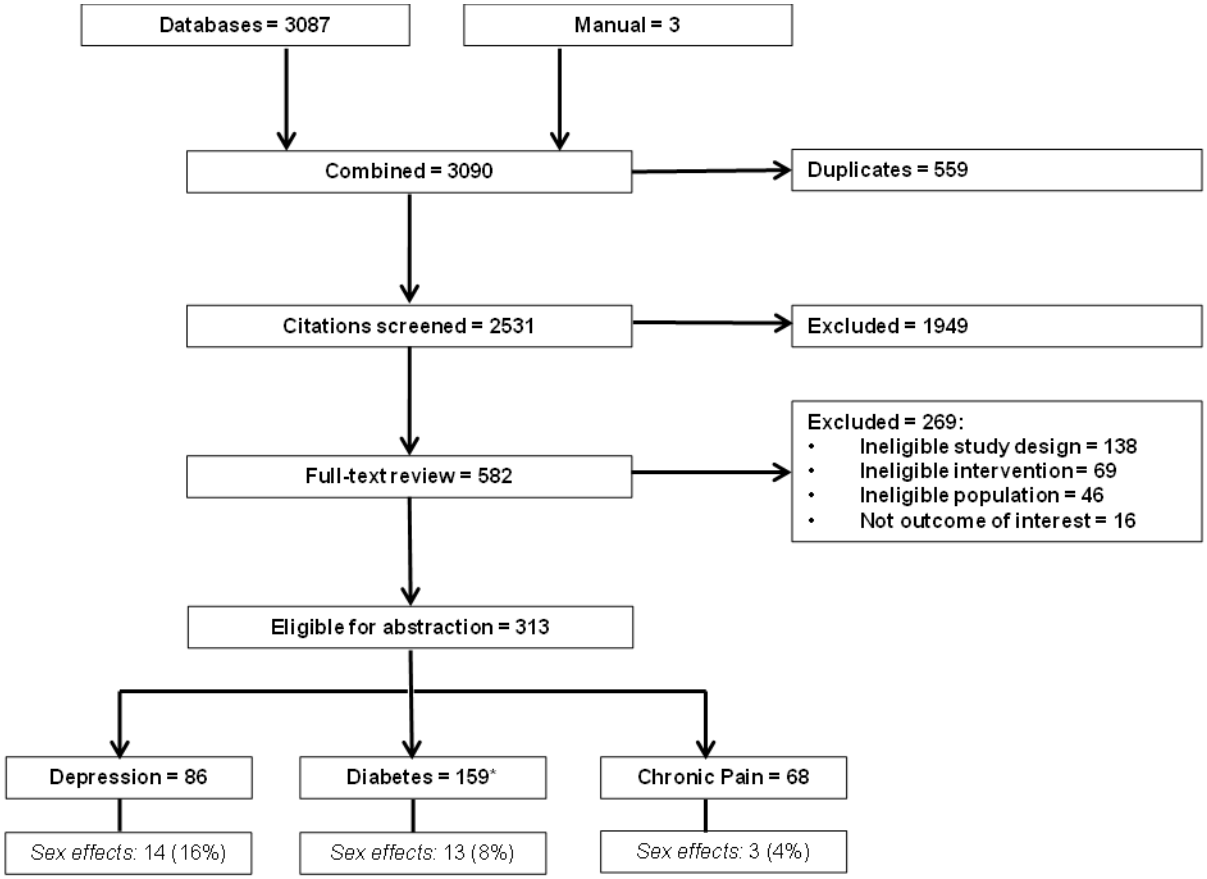
We organize the results into an overview describing the literature flow and key characteristics of the included systematic reviews, followed by brief executive summaries for each condition. In each summary, we describe the reviews, general applicability of results to women, and reporting of sex effects. Descriptions of overall treatment effects reported by reviews that did not conduct sex-specific analyses are summarized in Appendix E (depressive disorders), Appendix F (diabetes), and Appendix G (chronic pain).

LITERATURE FLOW

The literature search identified 2531 unique citations from a combined search of MEDLINE, the Cochrane Database of Systematic Reviews, and the bibliographies of umbrella reviews. After applying inclusion/exclusion criteria at the title-and-abstract screening level, 582 were retrieved for full-text review. Of these, 269 did not meet eligibility criteria. Of the 313 remaining eligible reviews, 45 diabetes reviews were examined for sex and gender terms and found to be negative; these 45 were not abstracted further. The remaining 268 systematic reviews were retained for full data abstraction (Figure 1).

Unless otherwise indicated by the specific term “study” or “RCT,” all results apply to these 268 systematic reviews, to which we refer to hereafter as “reviews.” Appendix B contains details of the search strategies, and Appendix H provides a full alphabetical bibliography of the reviews included for each condition.

Figure 1. Literature flow diagram



*We performed a keyword search for sex and gender terms on 45 of the 159 eligible diabetes reviews. The search was negative, which indicated sex or gender was not addressed in these articles. These 45 were thus not abstracted further, leaving 114 diabetes reviews for full data abstraction.

Of the 268 reviews that were fully abstracted, 86 addressed interventions for depression, 114 addressed interventions for type 2 diabetes, and 68 addressed interventions for the 3 types of chronic pain: CLBP (n=26), FM (n=34), and knee OA (n=8). Thirty-seven abstracted reviews (14%) originated from an organization known for high-quality reviews. There were more chronic pain reviews (25%) from these organizations than depression or diabetes reviews (11% each). The majority of abstracted reviews – 86% for depression, 61% for diabetes, and 84% for chronic pain – were restricted to RCTs.

Among fully abstracted reviews for all conditions other than fibromyalgia, only half (48%) summarized the gender distribution of the populations of the included studies. Sex effects were reported in only 30 of the 313 eligible reviews (10%) for all conditions. IPD meta-analysis—the method best suited to evaluating moderating variables such as gender—was rarely used (n=16 of 268 abstracted reviews, 6%)

DEPRESSIVE DISORDERS

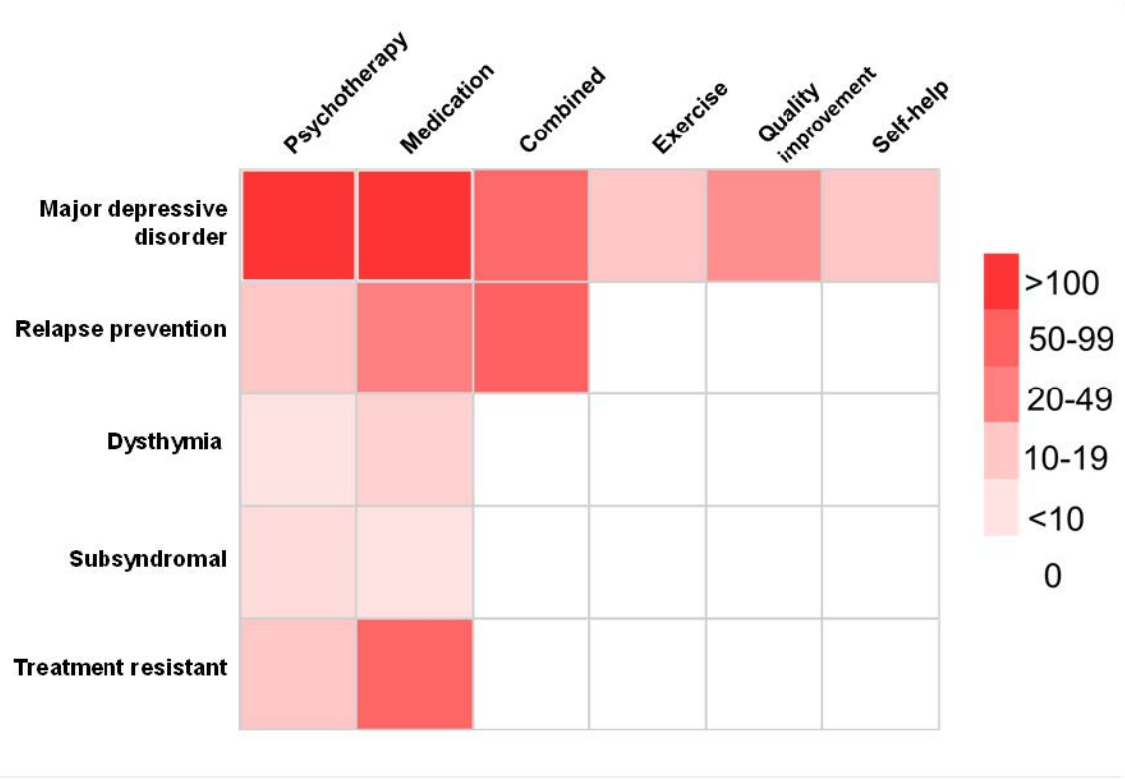
Overview

The 86 reviews most frequently evaluated interventions for a range of depressive disorders (n=43) or major depressive disorder alone (n=29). Reviews evaluating treatments for relapse prevention, treatment-resistant depression, persistent depressive disorder (dysthymia), and subsyndromal depression were much less frequent (n≤7 for each). The most frequently evaluated interventions were psychotherapy (n=44) and antidepressant medications (n=24). Four of the psychotherapy reviews evaluated internet-delivered therapy. Eight reviews evaluated the effects of combined psychotherapy and antidepressant medication, and 7 reviews evaluated exercise, including one focused on yoga. Quality improvement interventions and guided self-help were reviewed infrequently.

The eligible reviews included from 3 to 243 primary studies, and all but 13 reviews restricted inclusion to randomized controlled trials (RCTs). Nine reviews originated from an organization known for high-quality systematic reviews.[32-40] Fifty-two of 86 reviews (60%) reported the sex distribution of patients enrolled in the primary studies. When reported, women constituted the majority of participants for all of the interventions examined. However, relatively few of the recent, large systematic reviews evaluating psychotherapy or the combination of psychotherapy and antidepressants reported the sex distribution of the primary studies. Similarly, the minority of reviews addressing subsyndromal depression or relapse prevention reported the sex distribution of the primary studies.

Figure 2 shows a heat map of the number of primary studies evaluated in the largest review for each depressive condition–intervention dyad. Darker red indicates more primary studies and lighter red indicates fewer studies. Most reviews used quantitative analyses (*ie*, meta-analyses) to evaluate intervention effects. Ten reviews used IPD meta-analyses,[41-50] a statistical method that is particularly well-suited to evaluating moderator effects such as sex.

Figure 2. Number of primary studies included in largest review for each condition–intervention dyad

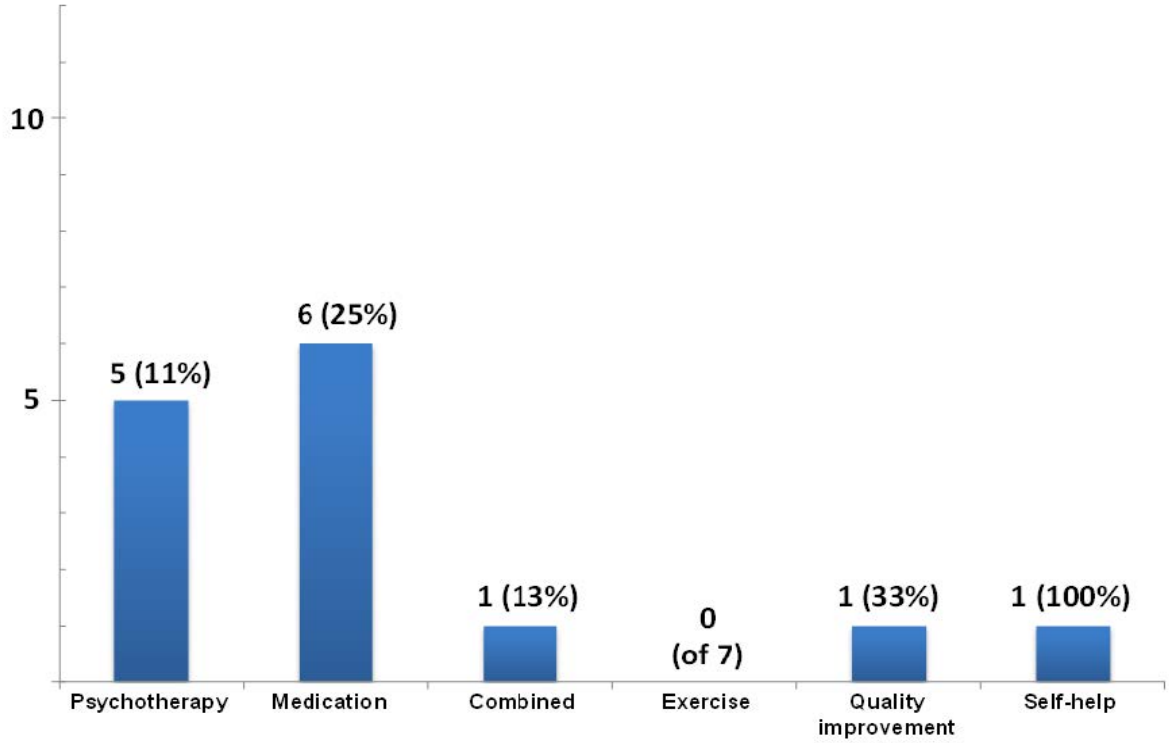


Note: Combined refers to medication plus psychotherapy.

Systematic Reviews: Reporting of Sex Effects for Depression Interventions

Of the 86 reviews, 14 (16%) reported results about sex effects (Figure 3). Sex effects were evaluated most frequently in reviews of antidepressant medications. One review focused on persistent depressive disorder,[51] and the remainder included a broad range of depressive disorders or major depressive disorder. Sex effects were explored using meta-regression and less frequently using qualitative analyses. Only 3 reviews[41,48,50] used IPD meta-analyses to explore sex effects. Next, we describe key findings from these reviews by depression intervention.

Figure 3. Number of reviews reporting sex effects for depression interventions



Note: Combined refers to medication plus psychotherapy.

Psychotherapy. Four reviews used meta-regression to evaluate sex effects.[37,52-54] In a review of 53 trials, cognitive behavioral therapy (CBT) was found to be more effective as the proportion of women enrolled in the trial increased, but the effect was small.[52] This finding was supported by another review,[54] but no differential sex effect was found when CBT was compared with pharmacotherapy.[37] Sex was not associated with treatment effects for short-term psychodynamic therapy.[53] A fifth review evaluated sex effects qualitatively.[55] This review identified a single study supporting greater efficacy for pharmacotherapy than psychotherapy for infertile women with depression (Hedges' g -0.94, CI -1.47 to -0.41).

Antidepressants. Six reviews reported sex effects.[34,48,50,56-58] In an IPD meta-analysis, women treated with duloxetine showed small additional benefit compared with men on the Sheehan Disability Scale (n=6; -0.99, CI -1.91 to -0.07).[48] Another IPD meta-analysis of desvenlafaxine trials reported that sex and baseline social impairment predicted some outcomes, but detailed results were not given.[50] A comprehensive review conducted by an EPC that used multiple treatment comparison meta-analyses did not show differences in antidepressant treatment effects as a class by age, sex, ethnicity, or comorbid conditions.[34] However, the authors noted that most studies did not address differences in efficacy or effectiveness between men and women. Limited data on adverse effects suggested that men treated with paroxetine were at higher risk for sexual dysfunction than women were, and that women receiving paroxetine compared with sertraline may be at higher risk for sexual dysfunction. Overall, adverse effects of antidepressants for men and women were similar.

Other reviews evaluated single drugs or antidepressants in older adults. A review restricted to sertraline and venlafaxine found that women showed small additional benefit compared with men when treated with venlafaxine.[58] One review used meta-regression to evaluate the association between the proportion of men enrolled and treatment effects.[56] In older adults with a depressive disorder, selective serotonin reuptake inhibitors (SSRIs) were somewhat less effective in men than in women at 3 of the 5 short-term follow-ups assessed.

Combined antidepressants and psychotherapy. A single review used meta-regression to evaluate the association between the proportion of women enrolled and the effects of combined treatments.[51] In patients with dysthymia, sex did not moderate the effect of psychotherapy plus antidepressants compared with antidepressants alone.

Quality improvement. One review using meta-regression analysis found no important difference between studies that enrolled a majority of females compared with a majority of males.[59]

Self-help. A single review used IPD meta-analysis to evaluate sex effects in primary care patients with a diagnosis of depression or elevated symptoms on a self-report scale.[41] Intervention effects did not vary by sex.

Other interventions. Sex effects were not examined in reviews of exercise or interventions for subsyndromal depression, interventions to prevent relapse, or interventions for treatment-resistant depression.

In summary, sex effects were examined infrequently, and the methodology most often employed (meta-regression) was suboptimal for drawing valid conclusions. Small sex effects were found for some antidepressants and psychotherapy, generally favoring better outcomes in women.

Primary Studies: Reporting of Sex Effects for Depression Interventions

We selected a sample of primary studies included in the eligible systematic reviews that randomized at least 75 patients per treatment arm to determine if these studies evaluated and reported treatment effects by sex. Reviews of quality improvement interventions[40] and psychotherapy[60] were used for this analysis because we did not identify any IPD meta-analyses for these high-priority interventions.

We examined 21 clinical trials evaluating collaborative care interventions (an approach to quality improvement) for depressive disorders. The number of patients randomized ranged from 153 to 1801. One trial enrolled only women,[61] and 5 enrolled Veterans.[62-66] Of the 21 trials, only 2 evaluated subgroup effects by sex and found no effect on outcomes.[67,68]

Ten of the 92 studies (11%) included in the review[60] randomized at least 75 patients to psychotherapy and to a comparator arm. Sample sizes in these studies ranged from 177 to 903. Two trials enrolled only women,[69,70] and none enrolled Veterans. Only one trial potentially evaluated sex as a moderator, stating “no demographic characteristic … moderated time to remission.”[71]

DIABETES

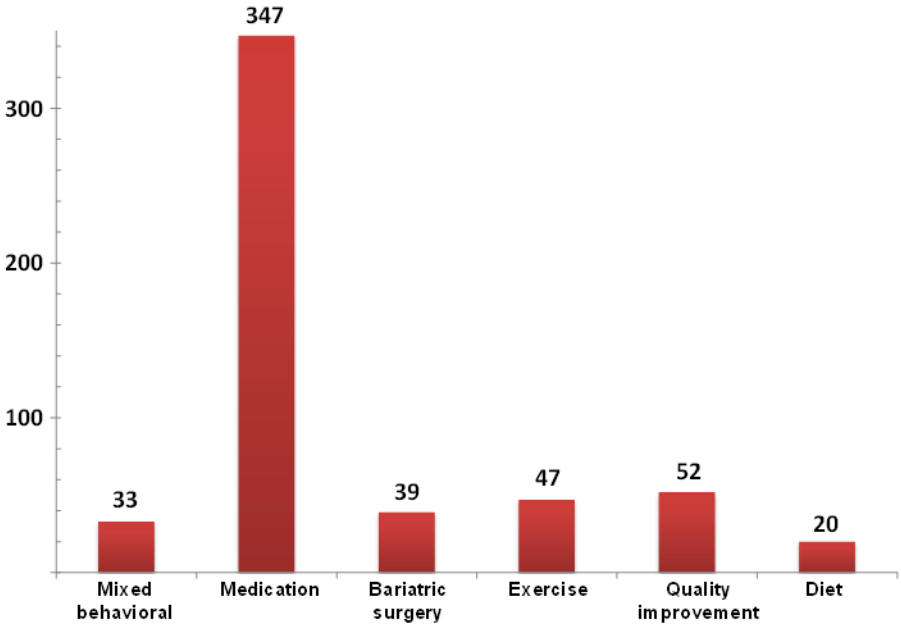
Overview

We conducted full data abstraction for 114 reviews evaluating diabetes. Of 159 eligible reviews, we examined all medication studies and prioritized for full abstraction those that were most likely pertinent and/or were positive by text searching for keywords related to sex effects. We fully abstracted reviews for all other interventions. Among all eligible reviews, the most frequently evaluated interventions were medications (n=120), while fewer examined exercise (n=14) and mixed psychoeducation and behavioral interventions (n=6). Twelve reviews examined the effects of bariatric surgery. Dietary (n=4) and quality improvement interventions (n=3) were reviewed less frequently.

Abstracted reviews included from 0 to 347 primary studies, and 70 (61%) were restricted to RCTs. Twelve reviews (10%) originated from an organization known for high-quality systematic reviews.[72-83] Figure 4 shows the number of primary studies evaluated in the largest systematic review for each intervention category. Most reviews (n=101; 89%) used quantitative analyses (*ie*, meta-analyses) to evaluate intervention effects. Only 5 reviews used IPD meta-analyses, and all of these evaluated medications.

Overall, 48 reviews (42%) reported the proportion of women included in primary studies, but this varied widely by intervention. Most reviews on bariatric surgery (n=9, 75%) provided information on inclusion of women, while about half of reviews on exercise (n=6, 43%) and mixed behavioral interventions (n=3, 50%) did so. Somewhat fewer medication reviews (n=30, 40%) reported on inclusion of women, and none did so for diet or quality improvement interventions.

Figure 4. Number of primary studies included in largest reviews of diabetes interventions

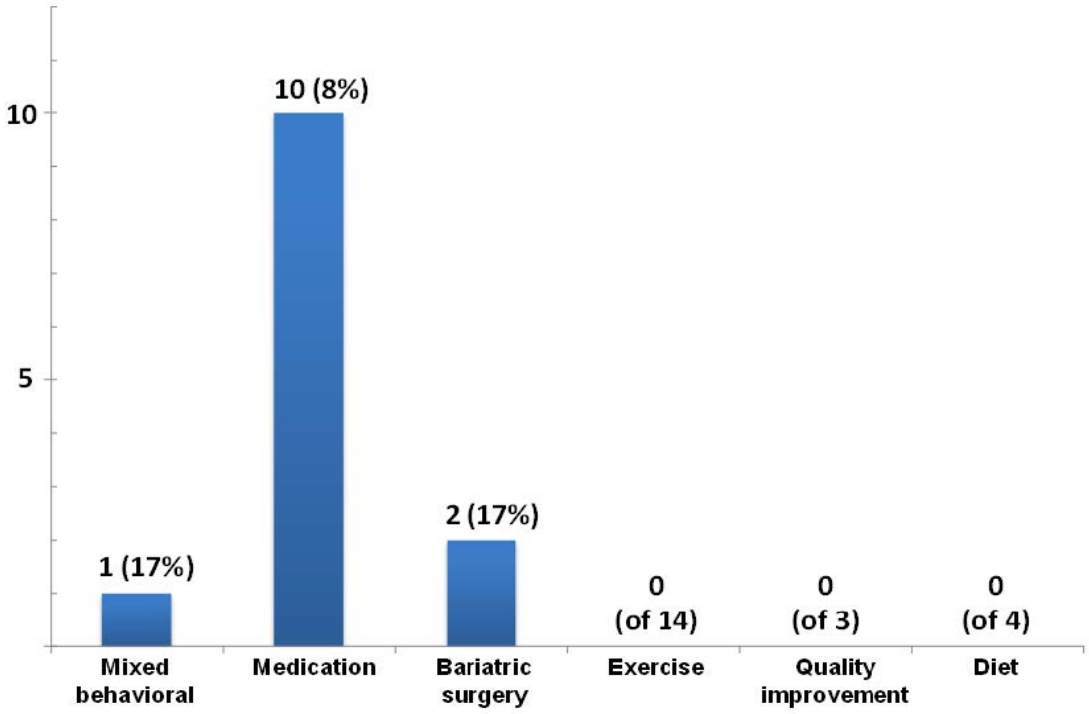


Systematic Reviews: Reporting of Sex Effects for Diabetes Interventions

Of the 159 eligible reviews, 13 (8%) reported results on sex effects (Figure 5). Additionally, 6 reviews examined the risk for various types of cancer associated with different diabetes medications (*eg*, metformin and insulin), and included estimates for breast cancer risk.[84-89] Finally, one review proposed to evaluate oral medications for women with preexisting diabetes or impaired glucose tolerance, but despite an adequate search strategy, found no eligible articles.[82]

Sex effects were reported most frequently in reviews of medications (n=10).[90-99] Two reviews examined sex effects on diabetic remission after bariatric surgery.[100,101] One review evaluated a range of psychoeducation interventions for minority women with diabetes and provided qualitative syntheses for various outcomes.[102] Sex effects were most often explored using meta-regression (n=8). Only 3 reviews[91,96,97] applied IPD meta-analyses to explore sex effects; all evaluated dipeptidyl peptidase-4 (DPP-4) inhibitors and included data only from industry-sponsored studies. Sex effects were not examined in reviews of supervised exercise, diet, or quality improvement. Next, we describe key findings from reviews reporting sex effects by diabetes intervention.

Figure 5. Number of reviews reporting sex effects for diabetes interventions



Psychoeducation and mixed behavioral interventions. Of 6 eligible reviews, one examined the effects of diabetes self-management education in black and Hispanic women, focusing on specific intervention features associated with positive results.[102] This review included 10 RCTs and 3 cohort studies with comparators. Qualitative syntheses were reported for multiple outcomes, including HbA1c (3 of 10 applicable studies showed positive effects). Intervention features were organized into 9 categories (*eg*, intervention setting, frequency of sessions, and mode of delivery). Multiple features in each category were associated with improvements in various outcomes.

Medications. Of 120 eligible reviews addressing medications, 10 reported sex effects.[90-99] Two focused exclusively on adverse effects, with one evaluating risk for bladder cancer associated with pioglitazone[92] and one evaluated fracture risk associated with sulfonylureas.[95] The review examining the risk of bladder cancer associated with pioglitazone found similar estimates of increased risk in men (HR 1.64, CI 1.01 to 2.67) and women (HR 1.69, CI 0.64 to 4.47), although only the results for men reached statistical significance.[92] The review on fracture risk associated with sulfonylureas included 21 eligible studies and reported results from a single RCT showing that there was decreased fracture risk for sulfonylureas compared with thiazolidinediones in women (RR 0.37, CI 0.23 to 0.61) but not in men (RR 0.85, CI 0.52-1.40).[95]

The remaining 8 reviews investigated various outcomes, including glycemic control, cardiovascular events and/or mortality, and risk for hypoglycemia.[90,91,93,94,96-99] Single reviews evaluated multiple classes of medications,[90] insulin therapy,[93] and metformin,[94] while 5 reviews addressed incretin mimetics.[91,96-99] The review on 8 medication classes included 218 RCTs; sex was evaluated as a source of heterogeneity and no association was found.[90] One review evaluated the effect of short-term intensive insulin therapy on b-cell function, insulin resistance, and long-term remission, and identified 7 eligible studies; the proportion of men was associated with study heterogeneity, and improvement in insulin resistance decreased with increasing male representation.[93] The review addressing the efficacy of metformin for preventing cardiovascular events and mortality included 35 RCTs and found no significant effect for cardiovascular events or survival.[94] However, when limiting the analysis to trials that evaluated metformin monotherapy (n=4), there was significantly decreased risk for all-cause mortality with metformin use (Mantel-Henzel OR 0.55, CI 0.36 to 0.89) and significantly increased benefit in trials with more women (slope -0.039, CI -0.076 to -0.003).[94]

Among 5 reviews examining incretin mimetics, one evaluated both glucagon-like peptide 1 receptor agonists and DPP-4 inhibitors, and included 38 RCTs.[99] This review examined hemoglobin A1c (HbA1c), weight, and hypoglycemia for exenatide, liraglutide, vildagliptin, and sitagliptin; adjusted analyses with key study information (*eg*, age, sex and study duration) did not change the results, and most covariates were not associated with significant effects.[99] One review of DPP-4 inhibitors included 43 RCTs and also evaluated glycemic control, weight, and hypoglycemia; multiple covariates (*eg*, sex and study duration) were employed in meta-regression and none had a significant effect.[98] Lastly, 3 reviews of DPP-4 inhibitors applied IPD meta-analyses to data from industry studies.[91,96,97] Using data from 8 RCTs, one review reported subgroup analyses showing different point estimates for risk of death from cardiovascular disease for men (HR 0.25, CI 0.10 to 0.60) and women (HR 0.96, CI 0.21 to 4.37) when comparing linagliptin with placebo, glimepiride, or voglibose.[97] Another review evaluated

linagliptin among participants with and without renal dysfunction and included data from 3 RCTs; both men and women had improved glycemic control with linagliptin, with no evidence of interaction effect for sex and treatment efficacy.[91] The third review examined risk of cardiovascular events with vildagliptin, utilizing data from 25 RCTs; overall, no significant associations were found between vildagliptin and risk for cardiovascular events among both men and women.[96]

Bariatric surgery. Of 12 reviews on bariatric surgery, 2 examined sex effects on diabetes remission after bariatric surgery; both found no significant associations.[100,101] Both reviews evaluated multiple types of bariatric surgery, included prospective and retrospective studies, and noted the generally low quality of included primary studies. One review included 39 studies, only 3 of which were RCTs; overall, diabetes remission rates varied significantly with the type of procedure (range 32.7% to 80.5% at 12 months) but not with age, sex, preoperative body mass index, or HbA1c.[100] This review also examined adverse events and complications following bariatric surgery but did not report sex-specific analyses for these outcomes.[100] The other review found 15 eligible studies and included data from 13 in meta-analyses evaluating the likelihood of diabetes remission; results showed decreased likelihood of remission with increasing age and diabetes duration but no significant associations with sex.[101]

In summary, sex effects were rarely examined, and reviews reporting sex results most often used meta-regression, a technique that is poorly suited to evaluating sex differences.[103,104] All IPD meta-analyses examining sex effects were on incretin mimetics and there were no significant sex effects for any outcome. Using meta-regression, one review found greater improvement of insulin resistance following short-term intensive insulin therapy in trials with more women; however, this physiologic outcome is of unclear clinical significance. No sex effects were found for diabetes remission after bariatric surgery. Multiple features of diabetes self-management education may be associated with positive effects in minority women.

Primary Studies: Reporting of Sex Effects for Diabetes Interventions

Reviews of dietary interventions,[105] mixed behavioral interventions,[106] and culturally tailored psychoeducation[83] were selected for further analysis of a sample of primary studies (see Methods) because we did not identify any IPD meta-analyses for these high-priority interventions.

Six of the 20 primary studies (30%) evaluating dietary interventions randomized at least 75 patients to each treatment arm.[107-112] Sample sizes in these studies ranged from 162 to 1224. One trial enrolled only women,[109] and none enrolled Veterans. Two RCTs evaluated sex as a moderator, and neither found a differential response for effects on weight[110] or HbA1c.[108]

Only 2 of 17 studies (12%) evaluating mixed behavioral interventions met the sample size requirement (n=182[113] and n=606[114]). These studies enrolled mixed samples of men and women, and did not describe Veteran enrollment. One study evaluated sex effects and found a greater effect of physical activity on glycemic control in men.[113]

Thirty-three clinical RCTs evaluated culturally tailored psychoeducation, and of these, 11 (33%) met the sample size requirement.[115-125] The number of patients randomized ranged from 201 to 567. Two RCTs enrolled only women,[116,117] and none enrolled Veterans. One study evaluated

sex effects and found no differential effect for HbA1c, fasting blood glucose, or diabetes knowledge.[115]

CHRONIC PAIN

Overview

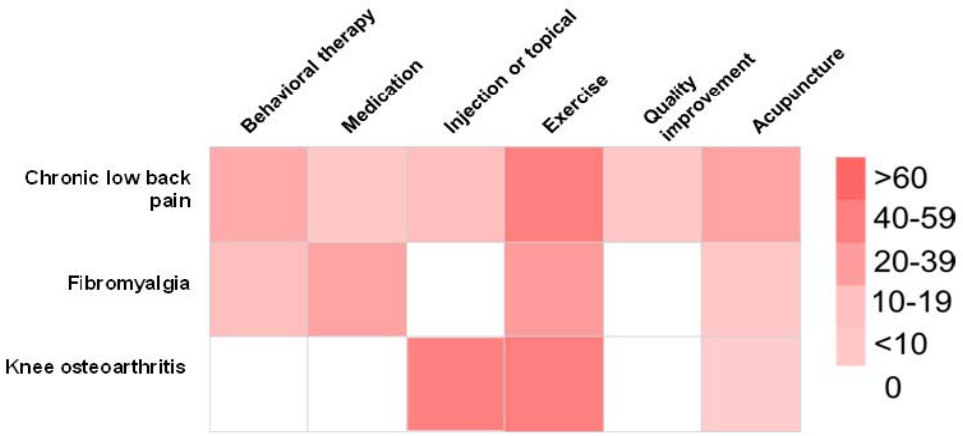
Three pain conditions were prioritized for review: chronic low back pain (CLBP), fibromyalgia (FM), and chronic knee pain due to osteoarthritis (knee OA). CLBP was limited to musculoskeletal or mechanical low back pain to differentiate it from inflammatory conditions for which specific treatments would be indicated.

Sixty-eight systematic reviews evaluated interventions specifically for CLBP (n=26), FM (n=34), and knee OA (n=8); one review evaluated acupuncture for both CLBP and knee OA. The most frequently evaluated interventions were exercise (n=21), medications (antidepressant, n=9; anticonvulsant, n=6; joint injection, n=5; and topical nonsteroidal anti-inflammatory drug, n=3), acupuncture and chiropractic manipulation (n=12), behavioral treatment (n=8), and combination interventions (n=4). One review on CLBP evaluated quality improvement interventions.

The eligible reviews included from 2 to 102 primary studies, and all but 11 reviews restricted inclusion to RCTs. Sixteen reviews originated from an organization known for high-quality systematic reviews. Figure 6 shows a heat map of the number of primary studies evaluated in the largest review for each chronic pain condition–intervention dyad. Most reviews used quantitative meta-analyses to evaluate intervention effects. One review used IPD meta-analyses.

The percentage of women included in the primary studies was reported in 8 of 26 reviews on CLBP and ranged from 45% to 100%.[126-133] For FM, the percentage of women included in the primary studies was reported in 23 of the 34 reviews on FM and ranged from 50% to 100% (median 95.5%). Five of 8 reviews of OA reported on the percentage of women, with the range being 50% to 100%.

Figure 6. Number of primary studies included in largest review for each condition–intervention dyad



Systematic Reviews: Reporting of Sex Effects for Chronic Pain Interventions

Of the 68 systematic reviews, only 3 (4%) reported results about sex effects. Sex effects were discussed in 2 reviews of CLBP[126,132] and one review of FM.[134] All of these reviews explored sex effects using meta-regression. We describe below key findings from reviews reporting sex effects for CLBP interventions, as well as some general findings from FM reviews.

Chronic low back pain. No review examined sex effects as a primary aim in CLBP; however, 2 evaluated sex effects using meta-regression. In a review evaluating the effectiveness of antidepressants and other medications for pain, sex was not associated with differences in treatment effect.[126] In a review examining quality improvement interventions, increasing proportion of women in the primary studies was associated with greater intervention effectiveness (beta=0.002; SE 0.001).[132]

Fibromyalgia. Only one review proposed to evaluate differential effects in men and women, but individual patient-level data were not available.[134] Also, we anticipated that analyses for sex effects would be difficult and require very large sample sizes, given that generally, more than 90% of the study participants were women. However, since women were the overwhelming majority of participants in trials for FM, reviews without sex specific analyses remain highly applicable to women. For this reason, we briefly outline results from FM reviews below, with more detailed results provided in Appendix G.

Of 34 eligible reviews, 14 examined medications (n=7 for antidepressants,[134-140] n=5 for anticonvulsant agents,[137,141-144] and n=2 for both classes[145,146]). The largest review of antidepressants addressed the effectiveness of duloxetine and milnacipran, and included 10 studies; there were small improvements in pain (SMD -0.23, CI -0.29 to -0.18), and quality of life (SMD -0.20, CI of -0.25 to -0.14).[134] Additional reviews that also evaluated these medications[136,137] found similar results. Reviews on anticonvulsants (*ie*, gabapentin and pregabalin) also showed improvement in pain.[137,141-144]

Six reviews evaluated various forms of exercise,[147-152] and while most of these showed some effectiveness for pain, there did not appear to be differences between different types of exercise (*eg*, aquatic vs land-based). Six reviews examined different types of psychotherapy or behavioral interventions.[153-158] A recent large review of CBT found low-quality evidence to support a small improvement in pain symptoms with CBT.[153] Five reviews examined acupoint stimulation/acupuncture[159-163] and found varying results depending on the type of comparator; compared with sham acupuncture, acupuncture did not significantly reduce FM-related pain. Two reviews on meditative movement therapies (*ie*, yoga, tai chi, and qigong) produced conflicting results, and it remains unclear if these therapies are beneficial.[149,151] One review examined chiropractic care and concluded that there was no significant difference between intervention and control groups.[164]

Knee OA. None of the 8 reviews for knee OA included plans for an analysis of sex effects either as a primary aim or as a subgroup analysis.[165-172]

Primary Studies: Reporting of Sex Effects for Chronic Pain Interventions

Reviews of knee OA[167] and behavioral interventions for CLBP[173] were selected for further analysis of a sample of primary studies (see Methods) because we did not identify any IPD meta-analyses for these high-priority interventions.

Thirty RCTs evaluated behavioral interventions for CLBP, and of these, 7 (23%) met the sample size requirement.[174-180] The number of patients randomized ranged from 161 to 409. No trials were limited to enrolling women and none reported on Veteran enrollment. None of the trials evaluated sex effects.

Eight of the 54 studies (15%) included in the review of exercise interventions for knee OA met the sample size requirement.[181-188] Sample sizes in these studies ranged from 182 to 439. No trials enrolled only women and none enrolled Veterans. Only one trial evaluated sex as a moderator, stating that "both sexes … showed similar improvement in self-reported disability, pain and 6-minute walk distance."[182]

SUMMARY: REPORTING OF SEX EFFECTS ACROSS ALL CONDITIONS

In Table 3, we summarize the key findings, across all conditions evaluated, of systematic reviews that address differential treatment effects between men and women. Overall, sex effects were evaluated more frequently in systematic reviews for depressive disorders. When differential treatment effects were identified, the differences between men and women were typically small.

Table 3. Summary of sex effects identified in systematic reviews

Condition	Possible differences in treatment effects between men and women	Possible lack of differences in treatment effects between men and women
Depressive disorders (Page 9)	Greater improvement in depressive symptoms CBT, duloxetine[a] SSRIs in older adults More adverse effects on sexual dysfunction Paroxetine	Depressive symptoms Antidepressants overall, quality improvement, self-help[a] Combined antidepressant and psychotherapy for dysthymia Adverse effects overall Antidepressants
Diabetes (Page 12)	Fracture risk Lower for sulfonylureas (compared with thiazolidinediones)	Glycemic control Linagliptin[a], vildagliptin[a] Weight loss Bariatric surgery
Chronic pain[b] (Page 17)	Greater improvement in CLBP Quality improvement	CLBP Antidepressants

[a] Findings are from individual patient data meta-analysis.
[b] Fibromyalgia is not listed because studies predominantly enrolled women. Knee osteoarthritis is not listed because no reviews were identified.
Abbreviations: CBT=cognitive behavioral therapy; CLBP=chronic low back pain; SSRI=selective serotonin reuptake inhibitor

DISCUSSION

We identified 313 recently published systematic reviews evaluating eligible interventions for our 3 prioritized conditions. The most frequently evaluated interventions varied by condition: medications and psychotherapy for depression, medications for diabetes, and multiple interventions (*eg*, exercise, acupuncture or chiropractic manipulation, antidepressants) for the selected chronic pain conditions. For some eligible interventions in each condition, we were unable to find current reviews. Most reviews limited eligibility to RCTs, and the number of primary studies included ranged from 0 to 347. Systematic reviews varied in their reporting of the proportion of men and women enrolled in primary studies, ranging from a low of 31% of reviews for CLBP to a high of 60% of reviews for depressive disorders. When reported, women were well represented in primary studies for depression, and women predominated in the FM studies; representation in diabetes, CLBP, and knee OA studies was more variable.

Although systematic reviews were numerous, few evaluated sex as a moderator of treatment effects (16% for depressive disorders, 8% for diabetes, and 4% for chronic pain). Additionally, most reviews examining sex effects used meta-regression, a statistical technique that is subject to ecological fallacy and recommended only for moderators that are study design characteristics.[103,104] IPD meta-analysis is a more robust approach for evaluating sex effects, but it requires greater resources.[30] IPD meta-analysis was used by only a small fraction (n =16) of all included reviews. Table 4 summarizes the gaps in evidence on sex effects.

Table 4. Gaps in evidence on sex effects

Condition	Sex effects not examined	No IPD meta-analysis on sex effects
Depressive disorders	All interventions for relapse prevention, treatment-resistant depression and subsyndromal depression; exercise for any depressive disorder	Psychotherapy, combined antidepressants and psychotherapy, quality improvement
Diabetes	All nonpharmacologic interventions except bariatric surgery	All medications except DPP-4 inhibitors; all nonpharmacologic interventions
Chronic pain	CLBP All interventions except antidepressants and quality improvement Knee OA All interventions	CLBP All interventions Knee OA All interventions

Abbreviations: CLBP=chronic low back pain; DPP-4=dipeptidyl peptidase-4; OA=osteoarthritis

To better understand the feasibility of conducting new reviews comparing treatment effect estimates separately for men and women, we evaluated reports of primary RCTs for 7 different condition–intervention dyads. Overall, we found that a minority of RCTs had sample sizes large enough to examine moderator effects and that only 14% of these (9 of 66) examined interactions between sex and intervention groups. The paucity of RCTs examining sex effects is disappointing but is consistent with previous studies.[189,190]

To our knowledge, this is the first study to examine the evaluation of sex effects in systematic reviews. Our major finding is that, despite efforts to increase participation of women in trials and a greater focus on possible treatment differences between women and men, the sex distribution of included populations is summarized inconsistently, and evaluations for sex effects are rarely conducted. Thus, we urgently need to address the large gaps in our knowledge of sex differences in treatment effectiveness and adverse effects.

ACHIEVING ADEQUATE REPRESENTATION OF WOMEN IN CLINICAL STUDIES

In response to underrepresentation of women and minorities, the NIH Revitalization Act of 1993 established guidelines for the inclusion of women in all clinical research studies.[191] NIH and other research organizations have called for evaluation of sex effects at all stages of research, from the cellular level to human studies.[192] Increased understanding of sex effects can lead to improvements in clinical practice by informing whether sex and gender differences require tailoring of clinical interventions for optimal benefit among women. In a recent example, the U.S. Food and Drug Administration issued sex-specific dosage recommendations for zolpidem in 2013, in response to data about higher adverse effects in women using standard dosing.[193] When interventions are found to be differentially effective in men and women, it also provides impetus and rationale for research into more effective treatments for both sexes.

In order for the VA to ensure equitable benefit of VA research, it is important to evaluate sex effects and advance the scientific knowledge of evidence-based approaches to improving care for women Veterans. However, inclusion of women in VA research is particularly challenging because women remain a minority within the Veteran population, and the enrollment of women Veterans in VHA, while growing, remains a relatively low proportion (6.5% in 2012).[3] Additionally, multiple barriers exist to the recruitment and retention of women and minorities in clinical trials,[194] including fear and distrust of the research enterprise, lack of transportation, interference with work and/or family responsibilities, financial costs, and other burdens as a result of participation. Investing in methods to overcome these barriers will be important for VA.

Recognizing the needs and challenges associated with enrolling women, the VA established the Women's Health Research Network to facilitate research participation by women Veterans and encourage investigation of topics important for women Veterans' health.[195,196] This network is working to increase research capacity in VA by (1) informing VA investigators about issues important for women Veterans' health and health care, (2) providing training in oversampling techniques and subgroup analyses, and (3) developing a national practice-based research network to facilitate enrollment.[195,196]

PRIORITIZING AREAS FOR EVALUATION OF SEX EFFECTS

While evaluating sex effects is important, it can be costly. Examining moderator effects requires larger sample sizes, and the current lack of reporting on sex effects by clinical studies may be due in part to hesitance around identification of spurious subgroup effects in underpowered studies.[15] IPD meta-analysis could overcome small sample sizes in primary studies, but this requires cooperation and willingness to share data among investigators, more resources for data repositories, and adequate protections for patient privacy.[197] Therefore, the research community needs guiding principles for when information on sex effects is likely to be worth the additional

resources needed. We suggest several sources for consideration that could prompt designing new clinical studies to evaluate sex or gender effects:

- Basic science and early-phase clinical studies that suggest differential sex effects (*eg*, animal models, genomic evidence, pharmacokinetics);
- Observational studies or small RCTs that indicate differential effects; however, limitations in study design or statistical power decrease confidence in such findings;
- Effects of unique biological events, such as menopause, that may alter the risk of disease or response to therapies;
- Conceptual or theoretical models where knowledge of behavioral effects and other social science constructs strongly suggest a sex effect.

The following examples illustrate the application of these criteria. First, *antidepressants* are used for a wide range of conditions including depressive disorders and chronic pain syndromes. Pharmacokinetic evidence[198] supports different antidepressant doses for men and women. In the systematic reviews we evaluated, limited data suggested that adverse effects may differ for men and women with some antidepressants. Since adverse effects are a major cause of poor medication adherence, a better understanding of sex effects in adverse effects for different antidepressants could help clinicians tailor treatment.

Second, for diabetes interventions, *multiple medications* (*eg*, insulin and sulfonylureas) were associated with weight gain, but there was no evaluation of sex effects for this adverse outcome. There are many reasons why the effects of weight gain may be different between men and women, including physiologic, behavioral, and social factors.[199,200] Further, women may prioritize this outcome more than men, making knowledge of sex effects for weight gain particularly relevant for women.

Third, in examining the treatment of chronic pain, we found one review showing that *multicomponent interventions* for CLBP may be more effective in women. There are multiple reasons why these multifaceted interventions may have different efficacy in women when compared with men. One possibility is that such interventions lead to better incorporation and coordination of behavioral components, which may be more acceptable to women and even preferable over medications. For example, similar preferences for behavioral interventions have been found in the context of insomnia treatment for women Veterans.[201] Additionally, multicomponent interventions could more robustly manage comorbidities, such as sleep disorders and mental health diagnoses, which are more common among women and highly prevalent among women Veterans.[3,202] Thus, it would be valuable to confirm the presence of sex effects using IPD meta-analyses, as well as further evaluate the possibly differential role of key intervention components.

Additionally, it would be worthwhile to systematically evaluate how sex differences in preference for treatment type, including complementary and alternative treatments, would affect acceptability, adherence, and efficacy. Some work has shown that women Veterans may be more likely to prefer these treatments for pain,[202] but we are lacking information on how these preferences impact actual use and efficacy.

STUDY LIMITATIONS

Evidence maps are designed to give a broad overview of the evidence base. Our results are best used to describe areas where research has been conducted and where sex effects have been evaluated. However, we evaluated only systematic reviews published since 2009, so we may have missed older reviews of interventions. Also, we did not formally evaluate the quality of included reviews, and so our estimates of intervention effects should be considered preliminary. Reviews that found no evidence of differential intervention effects for men and women may have simply been underpowered to detect a clinically important difference. For IPD meta-analyses, we used an inclusive definition and allowed reviews that simply used available datasets, often from industry-sponsored trials, instead of requiring that such analyses systematically identify all eligible trials. When studies included in IPD meta-analyses are selected for convenience rather than systematically, selection bias can compromise the findings.

CONCLUSION

There is a large body of evidence for many of the examined interventions, particularly medications, psychotherapy, and exercise. However, systematic reviews and RCTs examined sex effects infrequently. When examined, sex effects generally favored greater benefits in women, but the differential effects were small and the analysis approaches were suboptimal. All RCTs and systematic reviews should report the proportion of men and women enrolled, and sex effects should be examined in adequately powered RCTs or IPD meta-analyses.

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