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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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STRUCTURED ABSTRACT

Background: Women are entering the military at unprecedented rates and comprise a rapidly increasing segment of Veterans Health Administration (VHA) enrollees. In response, the VHA Women's Health Service requested an evidence map to (1) identify effective interventions in women, (2) better understand sex differences in intervention effects for high-impact medical conditions, and (3) identify gaps in evidence about the efficacy of interventions in women.

Methods: We used a stakeholder-driven approach to identify high-priority conditions and interventions. From an initial list of 36 conditions, we used a forced-rank methodology to identify 3 conditions for evaluation: depressive disorders, type 2 diabetes mellitus, and chronic pain conditions (chronic low back pain [CLBP], chronic knee osteoarthritis [OA], and fibromyalgia [FM]). We evaluated treatments in broad categories, including medications, behavioral interventions, supervised exercise, and quality improvement interventions, along with certain condition-specific interventions. For each condition, we searched MEDLINE and the Cochrane Database of Systematic Reviews (CDSR) to identify relevant systematic reviews published from January 1, 2009, through October 31, 2014. Data abstracted from eligible systematic reviews included study design, 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, or results. For studies containing sex-specific results, we also abstracted the method used for evaluating sex effects (*eg*, meta-regression) and the outcomes that differed due to sex effects.

When information on sex effects was absent from eligible reviews, we selected high-priority interventions for further evaluation. For these interventions, we examined the largest recent systematic review to identify primary randomized controlled trials (RCTs) as candidates for review. We examined RCTs that randomized at least 75 patients per treatment arm to determine whether they reported sex effects. We chose this sample size criterion in order to limit evaluation to RCTs that had the potential for adequate statistical power to detect interaction effects (intervention * sex).

Results: A combined search of PubMed and CDSR yielded 2531 unique citations, of which 582 full-text articles were retrieved; 313 systematic reviews were eligible, and 268 were fully abstracted. Of these, 86 addressed interventions for depression, 114 addressed interventions for diabetes, and 68 addressed interventions for 3 types of chronic pain: CLBP (n=26), FM (n=34), and knee OA (n=8). Most reviews limited eligibility to RCTs, and the number of primary studies included in the systematic reviews ranged from 0 to 347. Only half (48%) of the reviews summarized the gender distribution of the populations of the included studies, but when summarized, women were well represented. Sex effects were reported in only 30 of the 313 (10%) eligible reviews: 14 (16%) for depressive disorders, 13 (8%) for diabetes, and 3 (4%) for chronic pain. Individual patient data (IPD) meta-analysis—the analysis method best suited to evaluating sex effects—was rarely used (n=16 of 268 abstracted reviews, 6%).

Overall, we found only a minority of RCTs had sample sizes large enough to examine moderator effects, and only 14% of these (9 of 66) examined interactions between sex and the main comparison, intervention type versus control group. When sex effects analyses were identified, most commonly no effect was found. Those with evidence of a sex effect often showed greater benefit in women (Table), but differential effects were typically small. There were important gaps in evidence on sex effects for multiple interventions in all conditions examined, either because no reviews evaluating sex effects were identified or because no IPD meta-analyses were identified.

Table. 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	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	Fracture risk Lower for sulfonylureas (compared with thiazolidinediones)	Glycemic control Linagliptin[a], vildagliptin[a] Weight loss Bariatric surgery
Chronic pain[b]	Greater improvement in CLBP Quality improvement	CLBP Antidepressants

[a] Findings are from IPD 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; OA=osteoarthritis; SSRI=selective serotonin reuptake inhibitor

Conclusions: There is a large body of evidence for many of the examined interventions, particularly medications, psychotherapy, and exercise. However, systematic reviews and primary 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 often 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.

ABBREVIATIONS TABLE

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
CLBP	Chronic low back pain
ES	Effect size
ESP	Evidence-based Synthesis Program
FM	Fibromyalgia
HSR&D	Health Services Research & Development
IPD	Individual-patient data
MD	Mean difference
MeSH	Medical Subject Heading
OA	Osteoarthritis
QUERI	Quality Enhancement Research Initiative
QI	Quality improvement
RCT	Randomized controlled trial
SMD	Standardized mean difference
SOE	Strength of evidence
VA	Veterans Affairs
VHA	Veterans Health Administration
WMD	Weighted mean difference

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EVIDENCE MAP

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

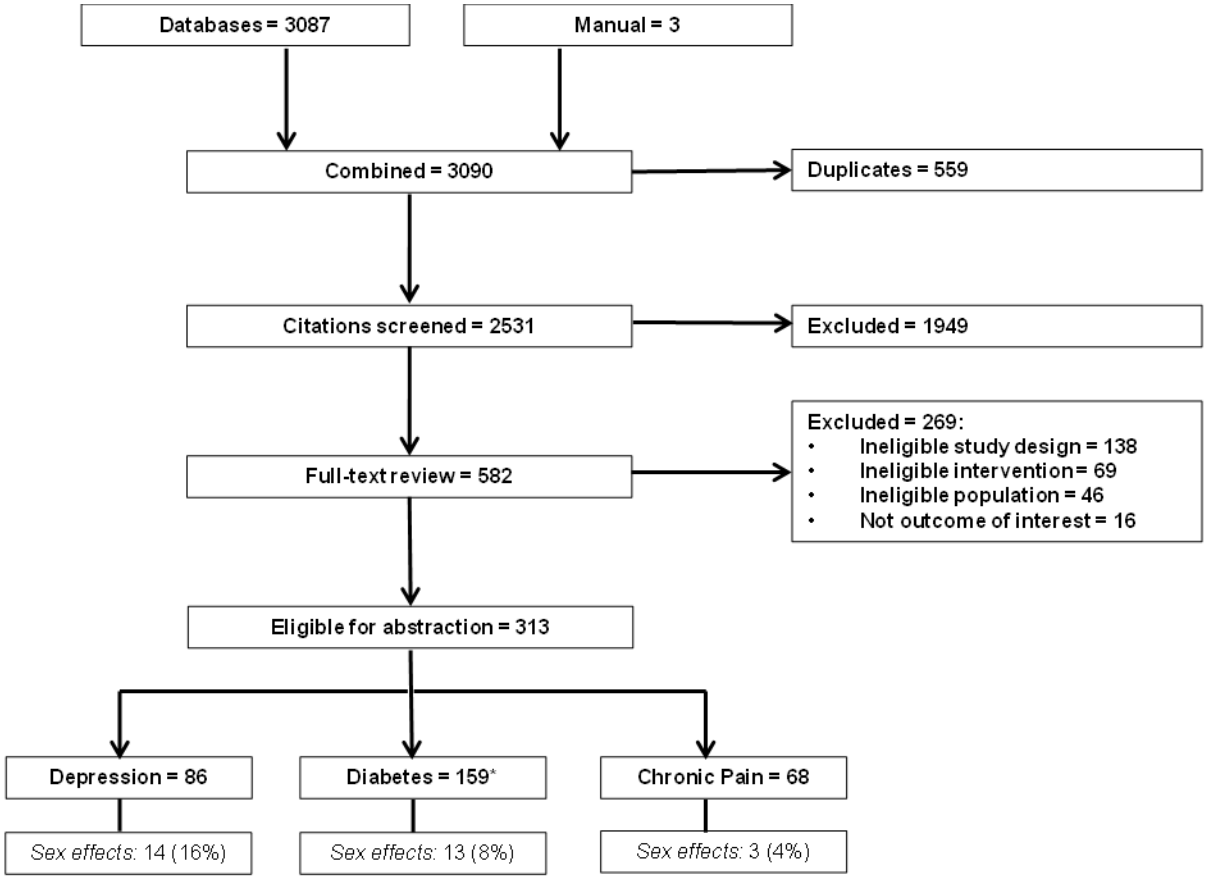
We organize the results into an overview describing the literature flow and key characteristics of the included systematic reviews, followed by brief executive summaries for each condition. In each summary, we describe the reviews, general applicability of results to women, and reporting of sex effects. 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

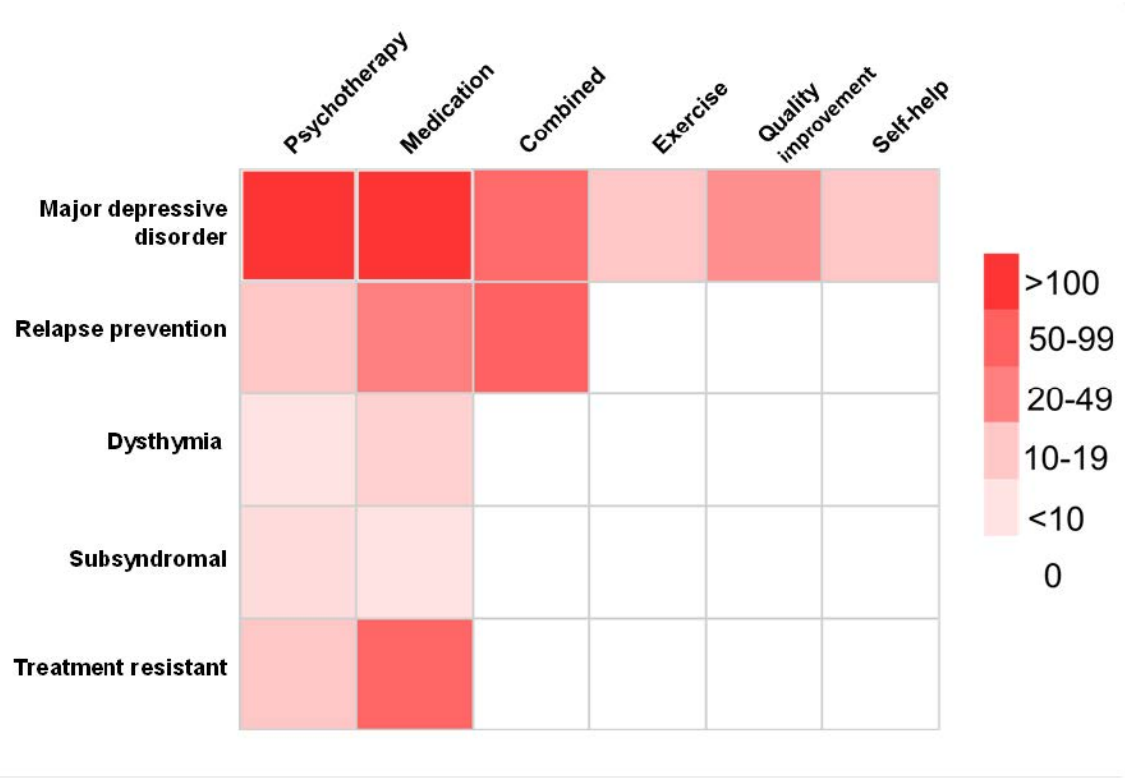
Overview

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

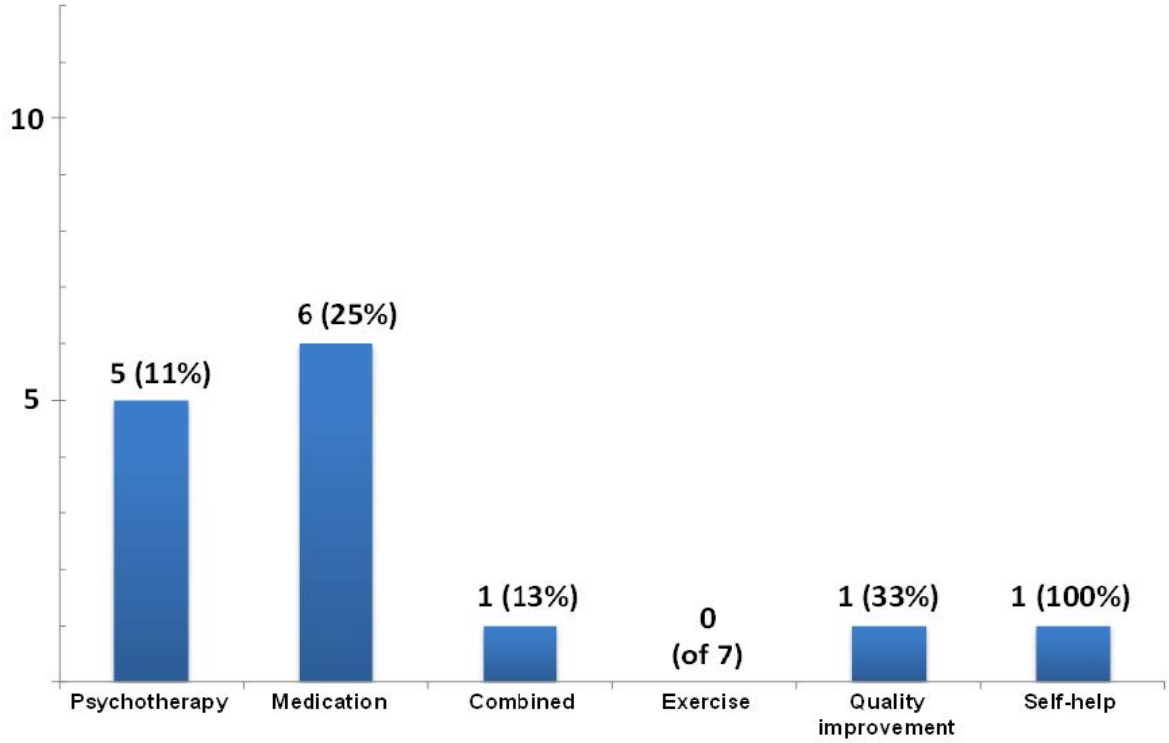


Note: Combined refers to medication plus psychotherapy.

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

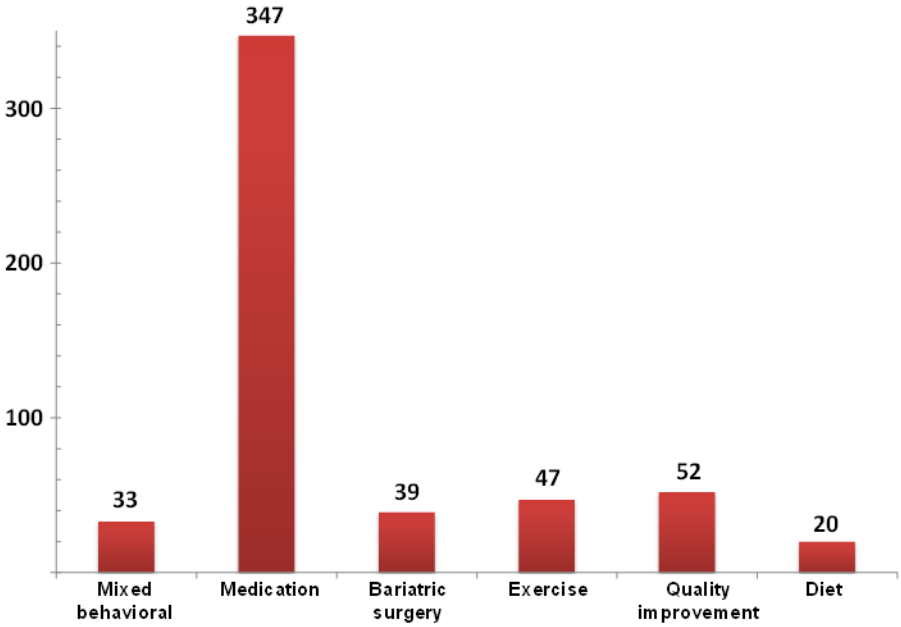
Overview

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

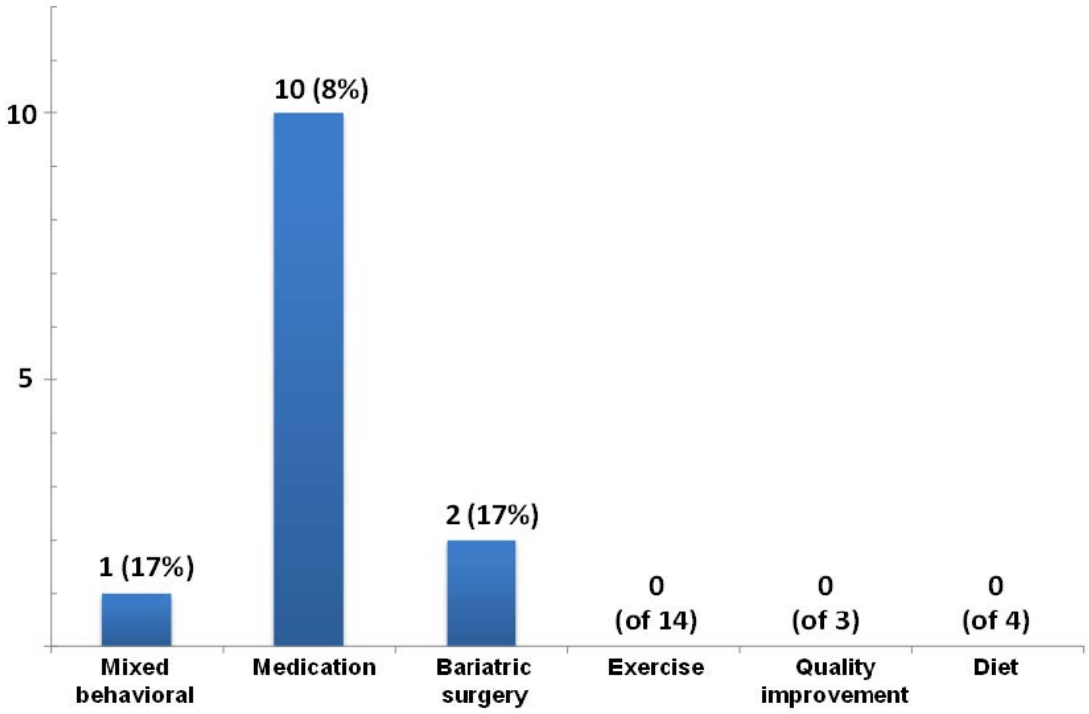


Systematic Reviews: Reporting of Sex Effects for Diabetes Interventions

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

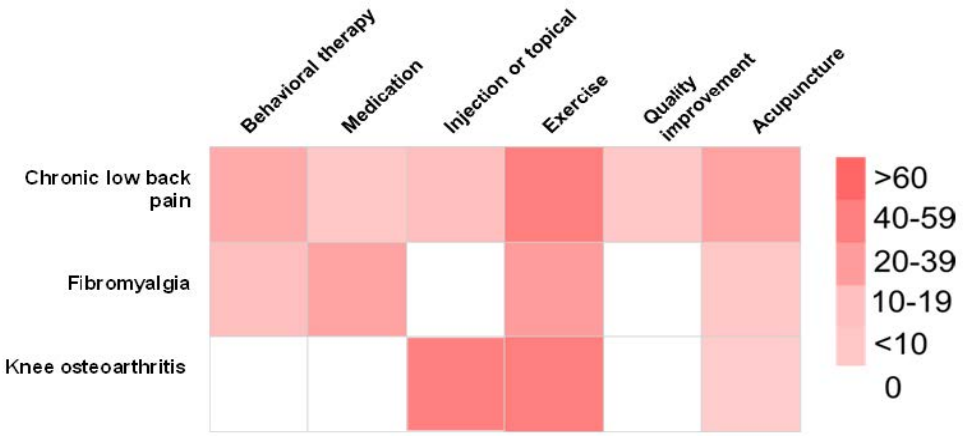
Three pain conditions were prioritized for review: chronic low back pain (CLBP), fibromyalgia (FM), and chronic knee pain due to osteoarthritis (knee OA). CLBP was limited to musculoskeletal or mechanical low back pain to differentiate it from inflammatory conditions for which specific treatments would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

REFERENCES

1. Yano EM, Hayes P, Wright S, et al. Integration of women veterans into VA quality improvement research efforts: what researchers need to know. *J Gen Intern Med.* 2010;25 Suppl 1:56-61.
2. Yano EM, Bastian LA, Bean-Mayberry B, et al. Using research to transform care for women veterans: advancing the research agenda and enhancing research-clinical partnerships. *Womens Health Issues.* 2011;21(4 Suppl):S73-83.
3. Frayne SM, Phibbs CS, Saechao F, et al. Sourcebook: Women Veterans in the Veterans Health Administration. Volume 3. Sociodemographics, Utilization, Costs of Care, and Health Profile. Women's Health Evaluation Initiative, Women's Health Services, Veterans Health Administration, Department of Veterans Affairs, Washington DC. February 2014.
4. Frayne SM, Parker VA, Christiansen CL, et al. Health status among 28,000 women veterans. The VA Women's Health Program Evaluation Project. *J Gen Intern Med.* 2006;21 Suppl 3:S40-46.
5. Frayne SM, Yu W, Yano EM, et al. Gender and use of care: planning for tomorrow's Veterans Health Administration. *J Womens Health (Larchmt).* 2007;16(8):1188-1199.
6. Skinner K, Sullivan LM, Tripp TJ, et al. Comparing the health status of male and female veterans who use VA health care: results from the VA Women's Health Project. *Women Health.* 1999;29(4):17-33.
7. Turner C, Frayne S. Veteran's Health Initiative: Military Sexual Trauma. Washington, DC: Department of Veterans Affairs Employee Education System and the Center for Women's Health. 2004. Available at: http://www.publichealth.va.gov/vethealthinitiative/sexual_trauma.asp. Accessed July 16, 2015.
8. Batuman F, Bean-Mayberry B, Goldzweig C, et al. VA Evidence-based Synthesis Program Reports. *Health Effects of Military Service on Women Veterans*. Washington (DC): Department of Veterans Affairs; 2011.
9. Kimerling R, Gima K, Smith MW, Street A, Frayne S. The Veterans Health Administration and military sexual trauma. *Am J Public Health.* 2007;97(12):2160-2166.
10. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. *JAMA.* 2003;289(4):397-400.
11. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes.* 2010;3(2):135-142.
12. Foulkes MA. After inclusion, information and inference: reporting on clinical trials results after 15 years of monitoring inclusion of women. *J Womens Health (Larchmt).* 2011;20(6):829-836.
13. Geller SE, Adams MG, Carnes M. Adherence to Federal Guidelines for Reporting of Sex and Race/Ethnicity in Clinical Trials. *J Womens Health (Larchmt).* 2006;15(10):1123-1131.
14. Blauwet LA, Hayes SN, McManus D, Redberg RF, Walsh MN. Low rate of sex-specific result reporting in cardiovascular trials. *Mayo Clin Proc.* 2007;82(2):166-170.
15. Bailey KR. Reporting of sex-specific results: a statistician's perspective. *Mayo Clin Proc.* 2007;82(2):158.

16. Prins MH, Smits KM, Smits LJ. Methodologic ramifications of paying attention to sex and gender differences in clinical research. *Gend Med.* 2007;4 Suppl B:S106-110.
17. Anthony M, Berg MJ. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: Part I. *J Womens Health Gend Based Med.* 2002;11(7):601-615.
18. Berlin JA, Ellenberg SS. Inclusion of women in clinical trials. *BMC Med.* 2009;7:56.
19. Yang Y, Carlin AS, Faustino PJ, et al. Participation of Women in Clinical Trials for New Drugs Approved by the Food and Drug Administration in 2000–2002. *J Womens Health (Larchmt).* 2009;18(3):303-310.
20. Ryan RE, Kaufman CA, Hill SJ. Building blocks for meta-synthesis: data integration tables for summarising, mapping, and synthesising evidence on interventions for communicating with health consumers. *BMC Med Res Methodol.* 2009;9:16.
21. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The Global Evidence Mapping Initiative: scoping research in broad topic areas. *BMC Med Res Methodol.* 2011;11:92.
22. Arksey H. Scoping the field: services for carers of people with mental health problems. *Health Soc Care Community.* 2003;11(4):335-344.
23. Chang SM, Carey TS, Kato EU, Guise JM, Sanders GD. Identifying research needs for improving health care. *Ann Intern Med.* 2012;157(6):439-445.
24. Centers for Disease Control and Prevention. National Hospital Ambulatory Medical Care Survey. Available at: http://www.cdc.gov/nchs/ahcd/about_ahcd.htm. Accessed February 3, 2015.
25. Centers for Disease Control and Prevention. Arthritis Among Veterans—United States, 2011–2013. Available: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6344a4.htm. Accessed February 3, 2015.
26. Centers for Disease Control and Prevention. National Hospital Ambulatory Medical Care Survey Factsheet Outpatient Department. Available: http://www.cdc.gov/nchs/data/ahcd/NHAMCS_2010_opd_factsheet.pdf. Accessed Febuary 5, 2015. 2010.
27. Murphy SL, Xu J, Kochanek KD. Division of Vital Statistics, "Deaths: Final Data for 2010," (Centers for Disease Control). Available: http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf. Accessed: Febuary 5, 2015. 2013;61(4).
28. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. http://seer.cancer.gov/. Accessed Febuary, 5 2015.
29. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med.* 2007;147(4):224-233.
30. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ.* 2010;340:c221.
31. Leon AC, Heo M. Sample sizes required to detect interactions between two binary fixed-effects in a mixed-effects linear regression model. *Comput Stat Data Anal.* 2009;53(3):603-608.
32. Churchill R, Moore TH, Furukawa TA, et al. "Third wave" cognitive and behavioural therapies versus treatment as usual for depression. *Cochrane Database Syst Rev.* 2013;10:Cd008705.

33. Cuijpers P, van Straten A, Bohlmeijer E, Hollon SD, Andersson G. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychol Med.* 2010;40(2):211-223.
34. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med.* 2011;155(11):772-785.
35. Hunot V, Moore TH, Caldwell DM, et al. "Third wave" cognitive and behavioural therapies versus other psychological therapies for depression. *Cochrane Database Syst Rev.* 2013;10:Cd008704.
36. Nieuwsma JA, Trivedi RB, McDuffie J, Kronish I, Benjamin D, Williams JW. Brief psychotherapy for depression: a systematic review and meta-analysis. *Int J Psychiatry Med.* 2012;43(2):129-151.
37. Roshanaei-Moghaddam B, Pauly MC, Atkins DC, Baldwin SA, Stein MB, Roy-Byrne P. Relative effects of CBT and pharmacotherapy in depression versus anxiety: is medication somewhat better for depression, and CBT somewhat better for anxiety? *Depress Anxiety.* 2011;28(7):560-567.
38. Shinohara K, Honyashiki M, Imai H, et al. Behavioural therapies versus other psychological therapies for depression. *Cochrane Database Syst Rev.* 2013;10:Cd008696.
39. Trivedi RB, Nieuwsma JA, Williams JW, Jr. Examination of the utility of psychotherapy for patients with treatment resistant depression: a systematic review. *J Gen Intern Med.* 2011;26(6):643-650.
40. Rubenstein LV, Williams JW, Jr., Danz M, Shekelle P, Suttorp M, Johnsen B. VA Evidence-based Synthesis Program Reports. *Determining Key Features of Effective Depression Interventions*. Washington (DC): Department of Veterans Affairs (US); 2009.
41. Bower P, Kontopantelis E, Sutton A, et al. Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. *BMJ.* 2013;346:f540.
42. Carpenter DJ, Fong R, Kraus JE, Davies JT, Moore C, Thase ME. Meta-analysis of efficacy and treatment-emergent suicidality in adults by psychiatric indication and age subgroup following initiation of paroxetine therapy: a complete set of randomized placebo-controlled trials. *J Clin Psychiatry.* 2011;72(11):1503-1514.
43. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA.* 2010;303(1):47-53.
44. Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. *Arch Gen Psychiatry.* 2012;69(6):572-579.
45. Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Arch Gen Psychiatry.* 2012;69(6):580-587.
46. Kasper S, Corruble E, Hale A, Lemoine P, Montgomery SA, Quera-Salva MA. Antidepressant efficacy of agomelatine versus SSRI/SNRI: results from a pooled analysis of head-to-head studies without a placebo control. *Int Clin Psychopharmacol.* 2013;28(1):12-19.
47. Kennedy SH, Andersen HF, Thase ME. Escitalopram in the treatment of major depressive disorder: a meta-analysis (Structured abstract). *Curr Med Res Opin.*

2009;25(1):161-175. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009105228/frame.html.

48. Mancini M, Sheehan DV, Demyttenaere K, et al. Evaluation of the effect of duloxetine treatment on functioning as measured by the Sheehan disability scale: pooled analysis of data from six randomized, double-blind, placebo-controlled clinical studies. *Int Clin Psychopharmacol.* 2012;27(6):298-309.

49. Papakostas GI, Culpepper L, Fayyad RS, Musgnung J, Guico-Pabia CJ. Efficacy of desvenlafaxine 50 mg compared with placebo in patients with moderate or severe major depressive disorder: a pooled analysis of six randomized, double-blind, placebo-controlled studies (Provisional abstract). *Database of Abstracts of Reviews of Effects.* 2013(4):312-321. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12013063325/frame.html.

50. Soares CN, Fayyad RS, Guico-Pabia CJ. Early improvement in depressive symptoms with desvenlafaxine 50 mg/d as a predictor of treatment success in patients with major depressive disorder. *J Clin Psychopharmacol.* 2014;34(1):57-65.

51. von Wolff A, Holzel LP, Westphal A, Harter M, Kriston L. Combination of pharmacotherapy and psychotherapy in the treatment of chronic depression: a systematic review and meta-analysis. *BMC Psychiatry.* 2012;12:61.

52. Braun SR, Gregor B, Tran US. Comparing bona fide psychotherapies of depression in adults with two meta-analytical approaches. *PLoS One.* 2013;8(6):e68135.

53. Driessen E, Cuijpers P, de Maat SC, Abbass AA, de Jonghe F, Dekker JJ. The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. *Clin Psychol Rev.* 2010;30(1):25-36.

54. Driessen E, Cuijpers P, Hollon SD, Dekker JJ. Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. *J Consult Clin Psychol.* 2010;78(5):668-680.

55. Cuijpers P, Reynolds CF, 3rd, Donker T, Li J, Andersson G, Beekman A. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. *Depress Anxiety.* 2012;29(10):855-864.

56. Calati R, Salvina Signorelli M, Balestri M, et al. Antidepressants in elderly: metaregression of double-blind, randomized clinical trials. *J Affect Disord.* 2013;147(1-3):1-8.

57. Carter GC, Cantrell RA, Victoria Z, et al. Comprehensive review of factors implicated in the heterogeneity of response in depression. *Depress Anxiety.* 2012;29(4):340-354.

58. Gibiino S, Marsano A, Serretti A. Specificity profile of venlafaxine and sertraline in major depression: metaregression of double-blind, randomized clinical trials (Provisional abstract). *International Journal of Neuropsychopharmacology.* 2014;17(1):1-8. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12014002430/frame.html.

59. Thota AB, Sipe TA, Byard GJ, et al. Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *Am J Prev Med.* 2012;42(5):525-538.

60. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *J Affect Disord.* 2014;159:118-126.

61. Araya R, Rojas G, Fritsch R, et al. Treating depression in primary care in low-income women in Santiago, Chile: a randomised controlled trial. *Lancet.* 2003;361(9362):995-1000.
62. Fortney JC, Pyne JM, Edlund MJ, et al. A randomized trial of telemedicine-based collaborative care for depression. *J Gen Intern Med.* 2007;22(8):1086-1093.
63. Hedrick SC, Chaney EF, Felker B, et al. Effectiveness of collaborative care depression treatment in Veterans' Affairs primary care. *J Gen Intern Med.* 2003;18(1):9-16.
64. Swindle RW, Rao JK, Helmy A, et al. Integrating clinical nurse specialists into the treatment of primary care patients with depression. *Int J Psychiatry Med.* 2003;33(1):17-37.
65. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA.* 2002;288(22):2836-2845.
66. Dobscha SK, Corson K, Hickam DH, Perrin NA, Kraemer DF, Gerrity MS. Depression decision support in primary care: a cluster randomized trial. *Ann Intern Med.* 2006;145(7):477-487.
67. Mann AH, Blizard R, Murray J, et al. An evaluation of practice nurses working with general practitioners to treat people with depression. *Br J Gen Pract.* 1998;48(426):875-879.
68. Simon GE, Ludman EJ, Tutty S, Operskalski B, Von Korff M. Telephone psychotherapy and telephone care management for primary care patients starting antidepressant treatment: a randomized controlled trial. *JAMA.* 2004;292(8):935-942.
69. Miranda J, Chung JY, Green BL, et al. Treating depression in predominantly low-income young minority women: a randomized controlled trial. *JAMA.* 2003;290(1):57-65.
70. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. *Lancet.* 2008;372(9642):902-909.
71. Frank E, Cassano GB, Rucci P, et al. Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. *Psychol Med.* 2011;41(1):151-162.
72. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med.* 2011;154(9):602-613.
73. Cleveringa FG, Gorter KJ, van den Donk M, van Gijsel J, Rutten GE. Computerized decision support systems in primary care for type 2 diabetes patients only improve patients' outcomes when combined with feedback on performance and case management: a systematic review. *Diabetes Technol Ther.* 2013;15(2):180-192.
74. Cramer H, Lauche R, Haller H, Steckhan N, Michalsen A, Dobos G. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. *Int J Cardiol.* 2014;173(2):170-183.
75. Egginton JS, Ridgeway JL, Shah ND, et al. Care management for Type 2 diabetes in the United States: a systematic review and meta-analysis. *BMC Health Serv Res.* 2012;12:72.
76. Hemmingsen B, Schroll JB, Lund SS, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2013;4:Cd009008.
77. Lee NJ, Norris SL, Thakurta S. Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. *Ann Fam Med.* 2010;8(6):542-549.

78. Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2010(1):Cd002967.
79. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med.* 2013;159(8):543-551.
80. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2011(10):Cd006423.
81. Sumamo E, Ha C, Korownyk C, Vandermeer B, Dryden DM. AHRQ Technology Assessments. *Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
82. Tieu J, Coat S, Hague W, Middleton P. Oral anti-diabetic agents for women with pre-existing diabetes mellitus/impaired glucose tolerance or previous gestational diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2010(10). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007724.pub2/abstract.
83. Attridge M, Creamer J, Ramsden M, Cannings-John R, Hawthorne K. Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2014(9). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006424.pub3/abstract.
84. Bosetti C, Rosato V, Buniato D, Zambon A, La Vecchia C, Corrao G. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. *Oncologist.* 2013;18(2):148-156.
85. Col NF, Ochs L, Springmann V, Aragaki AK, Chlebowski RT. Metformin and breast cancer risk: a meta-analysis and critical literature review. *Breast Cancer Res Treat.* 2012;135(3):639-646.
86. Colmers IN, Bowker SL, Tjosvold LA, Johnson JA. Insulin use and cancer risk in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies. *Diabetes Metab.* 2012;38(6):485-506.
87. Decensi A, Puntoni M, Goodwin P, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila).* 2010;3(11):1451-1461.
88. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. *PLoS One.* 2013;8(8):e71583.
89. Soranna D, Scotti L, Zambon A, et al. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist.* 2012;17(6):813-822.
90. Esposito K, Chiodini P, Bellastella G, Maiorino MI, Giugliano D. Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. *Diabetes Obes Metab.* 2012;14(3):228-233.
91. Groop PH, Del Prato S, Taskinen MR, et al. Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. *Diabetes Obes Metab.* 2014;16(6):560-568.
92. He S, Tang YH, Zhao G, Yang X, Wang D, Zhang Y. Pioglitazone prescription increases risk of bladder cancer in patients with type 2 diabetes: an updated meta-analysis. *Tumour Biol.* 2014;35(3):2095-2102.

93. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2013;1(1):28-34.
94. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 2011;13(3):221-228.
95. Lapane KL, Yang S, Brown MJ, Jawahar R, Pagliasotti C, Rajpathak S. Sulfonylureas and risk of falls and fractures: a systematic review. *Drugs Aging.* 2013;30(7):527-547.
96. Schweizer A, Dejager S, Foley JE, Couturier A, Ligueros-Saylan M, Kothny W. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population. *Diabetes Obes Metab.* 2010;12(6):485-494.
97. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle HJ. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. *Cardiovasc Diabetol.* 2012;11:3.
98. Esposito K, Cozzolino D, Bellastella G, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2011;13(7):594-603.
99. Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. *Pharmacology.* 2010;86(1):44-57.
100. Parikh M, Issa R, Vieira D, et al. Role of bariatric surgery as treatment for type 2 diabetes in patients who do not meet current NIH criteria: a systematic review and meta-analysis. *J Am Coll Surg.* 2013;217(3):527-532.
101. Wang GF, Yan YX, Xu N, et al. Predictive Factors of Type 2 Diabetes Mellitus Remission Following Bariatric Surgery: a Meta-analysis. *Obes Surg.* 2015;25(2):199-208.
102. Gucciardi E, Chan VW, Manuel L, Sidani S. A systematic literature review of diabetes self-management education features to improve diabetes education in women of Black African/Caribbean and Hispanic/Latin American ethnicity. *Patient Educ Couns.* 2013;92(2):235-245.
103. Chapter 9: Analysing data and undertaking meta-analyses. Editors: Jonathan J Deeks, Julian PT Higgins and Douglas G Altman on behalf of the Cochrane Statistical Methods Group. Available at: http://handbook.cochrane.org/chapter_9/9_analysing_data_and_undertaking_meta_analyses.htm. Accessed July 31, 2015.
104. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed July 16, 2015.
105. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr.* 2013;97(3):505-516.
106. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care.* 2012;35(12):2681-2689.

107. Salas-Salvado J, Fernandez-Ballart J, Ros E, et al. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med.* 2008;168(22):2449-2458.
108. Jenkins DJ, Kendall CW, McKeown-Eyssen G, et al. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA.* 2008;300(23):2742-2753.
109. Toobert DJ, Glasgow RE, Strycker LA, et al. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: a randomized clinical trial. *Diabetes Care.* 2003;26(8):2288-2293.
110. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med.* 2009;151(5):306-314.
111. Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes Obes Metab.* 2010;12(3):204-209.
112. Wolever TM, Gibbs AL, Mehling C, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr.* 2008;87(1):114-125.
113. Balducci S, Zanuso S, Nicolucci A, et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch Intern Med.* 2010;170(20):1794-1803.
114. Di Loreto C, Fanelli C, Lucidi P, et al. Validation of a counseling strategy to promote the adoption and the maintenance of physical activity by type 2 diabetic subjects. *Diabetes Care.* 2003;26(2):404-408.
115. Brown SA, Garcia AA, Kouzekanani K, Hanis CL. Culturally competent diabetes self-management education for Mexican Americans: the Starr County border health initiative. *Diabetes Care.* 2002;25(2):259-268.
116. Toobert DJ, Strycker LA, Barrera M, Jr., Osuna D, King DK, Glasgow RE. Outcomes from a multiple risk factor diabetes self-management trial for Latinas. *Ann Behav Med.* 2011;41(3):310-323.
117. Toobert DJ, Strycker LA, King DK, Barrera M, Jr., Osuna D, Glasgow RE. Long-term outcomes from a multiple-risk-factor diabetes trial for Latinas. *Transl Behav Med.* 2011;1(3):416-426.
118. Hawthorne K, Tomlinson S. One-to-one teaching with pictures--flashcard health education for British Asians with diabetes. *Br J Gen Pract.* 1997;47(418):301-304.
119. Lorig K, Ritter PL, Villa F, Piette JD. Spanish diabetes self-management with and without automated telephone reinforcement: two randomized trials. *Diabetes Care.* 2008;31(3):408-414.
120. O'Hare JP, Raymond NT, Mughal S, et al. Evaluation of delivery of enhanced diabetes care to patients of South Asian ethnicity: the United Kingdom Asian Diabetes Study (UKADS). *Diabet Med.* 2004;21(12):1357-1365.
121. Rosal MC, Ockene IS, Restrepo A, et al. Randomized trial of a literacy-sensitive, culturally tailored diabetes self-management intervention for low-income latinos: latinos en control. *Diabetes Care.* 2011;34(4):838-844.

122. Crowley MJ, Powers BJ, Olsen MK, et al. The Cholesterol, Hypertension, And Glucose Education (CHANGE) study: results from a randomized controlled trial in African Americans with diabetes. *Am Heart J.* 2013;166(1):179-186.
123. Anderson RM, Funnell MM, Nwankwo R, Gillard ML, Oh M, Fitzgerald JT. Evaluating a problem-based empowerment program for African Americans with diabetes: results of a randomized controlled trial. *Ethn Dis.* 2005;15(4):671-678.
124. Bellary S, O'Hare JP, Raymond NT, et al. Enhanced diabetes care to patients of south Asian ethnic origin (the United Kingdom Asian Diabetes Study): a cluster randomised controlled trial. *Lancet.* 2008;371(9626):1769-1776.
125. Gary TL, Batts-Turner M, Yeh HC, et al. The effects of a nurse case manager and a community health worker team on diabetic control, emergency department visits, and hospitalizations among urban African Americans with type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med.* 2009;169(19):1788-1794.
126. Cawston H, Davie A, Paget MA, Skljarevski V, Happich M. Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain. *Eur Spine J.* 2013;22(9):1996-2009.
127. Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. *Clin J Pain.* 2013;29(5):450-460.
128. Holtzman S, Beggs RT. Yoga for chronic low back pain: a meta-analysis of randomized controlled trials. *Pain Res Manag.* 2013;18(5):267-272.
129. Lam M, Galvin R, Curry P. Effectiveness of acupuncture for nonspecific chronic low back pain: a systematic review and meta-analysis. *Spine (Phila Pa 1976).* 2013;38(24):2124-2138.
130. Meng XG, Yue SW. Efficacy of Aerobic Exercise for Treatment of Chronic Low Back Pain: A Meta-Analysis. *Am J Phys Med Rehabil.* 2014.
131. Ward L, Stebbings S, Cherkin D, Baxter GD. Yoga for functional ability, pain and psychosocial outcomes in musculoskeletal conditions: a systematic review and meta-analysis. *Musculoskeletal Care.* 2013;11(4):203-217.
132. Waterschoot FP, Dijkstra PU, Hollak N, de Vries HJ, Geertzen JH, Reneman MF. Dose or content? Effectiveness of pain rehabilitation programs for patients with chronic low back pain: a systematic review. *Pain.* 2014;155(1):179-189.
133. Wells C, Kolt GS, Marshall P, Hill B, Bialocerkowski A. The effectiveness of Pilates exercise in people with chronic low back pain: a systematic review. *PLoS One.* 2014;9(7):e100402.
134. Hauser W, Urrutia G, Tort S, Uceyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev.* 2013;1:Cd010292.
135. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2012;12:Cd008242.
136. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev.* 2014;1:Cd007115.
137. Derry S, Gill D, Phillips T, Moore RA. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2012;3:Cd008244.
138. Choy E, Marshall D, Gabriel ZL, Mitchell SA, Gylee E, Dakin HA. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. *Semin Arthritis Rheum.* 2011;41(3):335-345.e336.

139. Hauser W, Wolfe F, Tolle T, Uceyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. *CNS Drugs.* 2012;26(4):297-307.
140. Hauser W, Petzke F, Uceyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology (Oxford).* 2011;50(3):532-543.
141. Uceyler N, Sommer C, Walitt B, Hauser W. Anticonvulsants for fibromyalgia. *Cochrane Database Syst Rev.* 2013;10:Cd010782.
142. Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. *Rheumatology (Oxford).* 2010;49(4):706-715.
143. Tzellos TG, Toulis KA, Goulis DG, et al. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. *J Clin Pharm Ther.* 2010;35(6):639-656.
144. Moore RA, Straube S, Wiffen Philip J, Derry S, McQuay Henry J. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews.* 2009(3). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007076.pub2/abstract.
145. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain.* 2010;11(6):505-521.
146. Roskell NS, Beard SM, Zhao Y, Le TK. A meta-analysis of pain response in the treatment of fibromyalgia. *Pain Pract.* 2011;11(6):516-527.
147. Bidonde J, Busch AJ, Webber SC, et al. Aquatic exercise training for fibromyalgia. *Cochrane Database Syst Rev.* 2014;10:Cd011336.
148. Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther.* 2010;12(3):R79.
149. Langhorst J, Klose P, Dobos GJ, Bernardy K, Hauser W. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. *Rheumatol Int.* 2013;33(1):193-207.
150. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. *Cochrane Database Syst Rev.* 2013;12:Cd010884.
151. Mist SD, Firestone KA, Jones KD. Complementary and alternative exercise for fibromyalgia: a meta-analysis. *J Pain Res.* 2013;6:247-260.
152. Lima TB, Dias JM, Mazuquin BF, et al. The effectiveness of aquatic physical therapy in the treatment of fibromyalgia: a systematic review with meta-analysis. *Clin Rehabil.* 2013;27(10):892-908.
153. Bernardy K, Klose P, Busch AJ, Choy EH, Hauser W. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev.* 2013;9:Cd009796.
154. Bernardy K, Fuber N, Kollner V, Hauser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol.* 2010;37(10):1991-2005.
155. Lauche R, Cramer H, Dobos G, Langhorst J, Schmidt S. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. *J Psychosom Res.* 2013;75(6):500-510.
156. Veehof MM, Oskam MJ, Schreurs KM, Bohlmeijer ET. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *Pain.* 2011;152(3):533-542.

157. Glombiewski JA, Bernardy K, Hauser W. Efficacy of EMG- and EEG-Biofeedback in Fibromyalgia Syndrome: A Meta-Analysis and a Systematic Review of Randomized Controlled Trials. *Evid Based Complement Alternat Med.* 2013;2013:962741.
158. Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: a meta-analysis. *Pain.* 2010;151(2):280-295.
159. Yang B, Yi G, Hong W, et al. Efficacy of acupuncture on fibromyalgia syndrome: a meta-analysis. *J Tradit Chin Med.* 2014;34(4):381-391.
160. Cao H, Li X, Han M, Liu J. Acupoint stimulation for fibromyalgia: a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med.* 2013;2013:362831.
161. Deare JC, Zheng Z, Xue CC, et al. Acupuncture for treating fibromyalgia. *Cochrane Database Syst Rev.* 2013;5:Cd007070.
162. Cao H, Liu J, Lewith GT. Traditional Chinese Medicine for treatment of fibromyalgia: a systematic review of randomized controlled trials. *J Altern Complement Med.* 2010;16(4):397-409.
163. Langhorst J, Klose P, Musial F, Irnich D, Hauser W. Efficacy of acupuncture in fibromyalgia syndrome--a systematic review with a meta-analysis of controlled clinical trials. *Rheumatology (Oxford).* 2010;49(4):778-788.
164. Ernst E. Chiropractic treatment for fibromyalgia: a systematic review. *Clin Rheumatol.* 2009;28(10):1175-1178.
165. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. *Osteoarthritis Cartilage.* 2011;19(6):611-619.
166. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2012;9:Cd007400.
167. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2015;1:Cd004376.
168. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med.* 2012;172(19):1444-1453.
169. Avouac J, Vicaut E, Bardin T, Richette P. Efficacy of joint lavage in knee osteoarthritis: meta-analysis of randomized controlled studies. *Rheumatology (Oxford).* 2010;49(2):334-340.
170. Wallis JA, Taylor NF. Pre-operative interventions (non-surgical and non-pharmacological) for patients with hip or knee osteoarthritis awaiting joint replacement surgery--a systematic review and meta-analysis. *Osteoarthritis Cartilage.* 2011;19(12):1381-1395.
171. Smith TO, King JJ, Hing CB. The effectiveness of proprioceptive-based exercise for osteoarthritis of the knee: a systematic review and meta-analysis. *Rheumatol Int.* 2012;32(11):3339-3351.
172. Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. *Arthroscopy.* 2013;29(12):2037-2048.
173. Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev.* 2010(7):Cd002014.
174. Fairbank J, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive

rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. *Bmj.* 2005;330(7502):1233.

175. Johnson RE, Jones GT, Wiles NJ, et al. Active exercise, education, and cognitive behavioral therapy for persistent disabling low back pain: a randomized controlled trial. *Spine (Phila Pa 1976).* 2007;32(15):1578-1585.

176. Poole H, Glenn S, Murphy P. A randomised controlled study of reflexology for the management of chronic low back pain. *Eur J Pain.* 2007;11(8):878-887.

177. Rose MJ, Reilly JP, Pennie B, Bowen-Jones K, Stanley IM, Slade PD. Chronic low back pain rehabilitation programs: a study of the optimum duration of treatment and a comparison of group and individual therapy. *Spine (Phila Pa 1976).* 1997;22(19):2246-2251; discussion 2252-2243.

178. Schweikert B, Jacobi E, Seitz R, et al. Effectiveness and cost-effectiveness of adding a cognitive behavioral treatment to the rehabilitation of chronic low back pain. *J Rheumatol.* 2006;33(12):2519-2526.

179. Smeets RJ, Vlaeyen JW, Hidding A, Kester AD, van der Heijden GJ, Knottnerus JA. Chronic low back pain: physical training, graded activity with problem solving training, or both? The one-year post-treatment results of a randomized controlled trial. *Pain.* 2008;134(3):263-276.

180. Von Korff M, Balderson BH, Saunders K, et al. A trial of an activating intervention for chronic back pain in primary care and physical therapy settings. *Pain.* 2005;113(3):323-330.

181. Hay EM, Foster NE, Thomas E, et al. Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: pragmatic randomised trial. *Bmj.* 2006;333(7576):995.

182. Ettinger WH, Jr., Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). *JAMA.* 1997;277(1):25-31.

183. Kao MJ, Wu MP, Tsai MW, Chang WW, Wu SF. The effectiveness of a self-management program on quality of life for knee osteoarthritis (OA) patients. *Arch Gerontol Geriatr.* 2012;54(2):317-324.

184. Hurley MV, Walsh NE, Mitchell HL, et al. Clinical effectiveness of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain: a cluster randomized trial. *Arthritis Rheum.* 2007;57(7):1211-1219.

185. Jenkinson CM, Doherty M, Avery AJ, et al. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. *Bmj.* 2009;339:b3170.

186. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum.* 2004;50(5):1501-1510.

187. O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Ann Rheum Dis.* 1999;58(1):15-19.

188. Yip YB, Sit JW, Fung KK, et al. Impact of an Arthritis Self-Management Programme with an added exercise component for osteoarthritic knee sufferers on improving pain, functional outcomes, and use of health care services: An experimental study. *Patient Educ Couns.* 2007;65(1):113-121.

189. Kim ESH, Carrigan TP, Menon V. Enrollment of Women in National Heart, Lung, and Blood Institute-Funded Cardiovascular Randomized Controlled Trials Fails to Meet Current Federal Mandates for Inclusion. *J Am Coll Cardiol.* 2008;52(8):672-673.
190. Johnson SM, Karvonen CA, Phelps CL, Nader S, Sanborn BM. Assessment of analysis by gender in the Cochrane reviews as related to treatment of cardiovascular disease. *J Womens Health (Larchmt).* 2003;12(5):449-457.
191. National Institutes of Health. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001. Available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Accessed July 27, 2015.
192. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature.* 2014;509(7500):282-283.
193. Farkas RH, Unger EF, Temple R. Zolpidem and driving impairment—identifying persons at risk. *N Engl J Med.* 2013;369(8):689-691.
194. National Institutes of Health. NIH Office of Research on Women's Health. Inclusion of Women and Minorities in Clinical Research. Available at: http://orwh.od.nih.gov/research/inclusion/index.asp. Accessed July 27, 2015.
195. Frayne SM, Carney DV, Bastian L, et al. The VA Women's Health Practice-Based Research Network: amplifying women veterans' voices in VA research. *J Gen Intern Med.* 2013;28 Suppl 2:S504-509.
196. Yano EM. A partnered research initiative to accelerate implementation of comprehensive care for women veterans: the VA women's health CREATE. *Med Care.* 2015;53(4 Suppl 1):S10-14.
197. Hudson KL, Collins FS. Sharing and reporting the results of clinical trials. *JAMA.* 2015;313(4):355-356.
198. Kokras N, Dalla C, Papadopoulou-Daifoti Z. Sex differences in pharmacokinetics of antidepressants. *Expert Opin Drug Metab Toxicol.* 2011;7(2):213-226.
199. Liu H, Umberson D. Gender, stress in childhood and adulthood, and trajectories of change in body mass. *Soc Sci Med.* 2015;139:61-69.
200. Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr.* 2008;99(5):931-940.
201. Hughes J, Jouldjian S, Washington DL, Alessi CA, Martin JL. Insomnia and symptoms of post-traumatic stress disorder among women veterans. *Behav Sleep Med.* 2013;11(4):258-274.
202. Bielawski MP, Goldstein KM, Mattocks KM, Bean-Mayberry B, Yano EM, Bastian LA. Improving care of chronic conditions for women veterans: identifying opportunities for comparative effectiveness research. *J Comp Eff Res.* 2014;3(2):155-166.
203. Ramsberg J, Asseburg C, Henriksson M. Effectiveness and cost-effectiveness of antidepressants in primary care: a multiple treatment comparison meta-analysis and cost-effectiveness model. *PLoS One.* 2012;7(8):e42003.
204. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry.* 2011;72(4):509-514.
205. Machado M, Einarson TR. Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials (Structured abstract). *Journal of Clinical Pharmacy and Therapeutics.* 2010;35(2):177-188.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010002896/frame.html.

206. Rocha FL, Fuzikawa C, Riera R, Hara C. Combination of antidepressants in the treatment of major depressive disorder: a systematic review and meta-analysis. *J Clin Psychopharmacol.* 2012;32(2):278-281.

207. Schueler YB, Koesters M, Wieseler B, et al. A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. *Acta Psychiatr Scand.* 2011;123(4):247-265.

208. Tedeschini E, Levkovitz Y, Iovieno N, Ameral VE, Nelson JC, Papakostas GI. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *J Clin Psychiatry.* 2011;72(12):1660-1668.

209. Baardseth TP, Goldberg SB, Pace BT, et al. Cognitive-behavioral therapy versus other therapies: redux. *Clin Psychol Rev.* 2013;33(3):395-405.

210. Cuijpers P, de Beurs DP, van Spijker BA, Berking M, Andersson G, Kerkhof AJ. The effects of psychotherapy for adult depression on suicidality and hopelessness: a systematic review and meta-analysis. *J Affect Disord.* 2013;144(3):183-190.

211. Cuijpers P, Smit F, Bohlmeijer E, Hollon SD, Andersson G. Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. *Br J Psychiatry.* 2010;196(3):173-178.

212. Cuijpers P, Koole SL, van Dijke A, Roca M, Li J, Reynolds CF, 3rd. Psychotherapy for subclinical depression: meta-analysis. *Br J Psychiatry.* 2014;205(4):268-274.

213. Cuijpers P, Turner EH, Mohr DC, et al. Comparison of psychotherapies for adult depression to pill placebo control groups: a meta-analysis. *Psychol Med.* 2014;44(4):685-695.

214. Cuijpers P, Geraedts AS, van Oppen P, Andersson G, Markowitz JC, van Straten A. Interpersonal psychotherapy for depression: a meta-analysis. *Am J Psychiatry.* 2011;168(6):581-592.

215. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF, 3rd. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. *World Psychiatry.* 2013;12(2):137-148.

216. Gould RL, Coulson MC, Howard RJ. Cognitive behavioral therapy for depression in older people: a meta-analysis and meta-regression of randomized controlled trials. *J Am Geriatr Soc.* 2012;60(10):1817-1830.

217. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol.* 2010;78(2):169-183.

218. Jakobsen JC, Lindschou Hansen J, Storebo OJ, Simonsen E, Gluud C. The effects of cognitive therapy versus 'treatment as usual' in patients with major depressive disorder. *PLoS One.* 2011;6(8):e22890.

219. Jakobsen JC, Hansen JL, Simonsen S, Simonsen E, Gluud C. Effects of cognitive therapy versus interpersonal psychotherapy in patients with major depressive disorder: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. *Psychol Med.* 2012;42(7):1343-1357.

220. Jakobsen JC, Hansen JL, Simonsen E, Gluud C. The effect of interpersonal psychotherapy and other psychodynamic therapies versus 'treatment as usual' in patients with major depressive disorder. *PLoS One.* 2011;6(4):e19044.

221. Jakobsen JC, Hansen JL, Storebo OJ, Simonsen E, Gluud C. The effects of cognitive therapy versus 'no intervention' for major depressive disorder. *PLoS One.* 2011;6(12):e28299.
222. Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: a comprehensive meta-analysis. *Clin Psychol Rev.* 2013;33(6):763-771.
223. Kiosses DN, Leon AC, Arean PA. Psychosocial interventions for late-life major depression: evidence-based treatments, predictors of treatment outcomes, and moderators of treatment effects. *Psychiatr Clin North Am.* 2011;34(2):377-401, viii.
224. Krishna M, Jauhari A, Lepping P, Turner J, Crossley D, Krishnamoorthy A. Is group psychotherapy effective in older adults with depression? A systematic review. *Int J Geriatr Psychiatry.* 2011;26(4):331-340.
225. Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychol Med.* 2010;40(1):9-24.
226. Okumura Y, Ichikura K. Efficacy and acceptability of group cognitive behavioral therapy for depression: a systematic review and meta-analysis. *J Affect Disord.* 2014;164:155-164.
227. Samad Z, Brealey S, Gilbody S. The effectiveness of behavioural therapy for the treatment of depression in older adults: a meta-analysis. *Int J Geriatr Psychiatry.* 2011;26(12):1211-1220.
228. Spielmans GI, Berman MI, Usitalo AN. Psychotherapy versus second-generation antidepressants in the treatment of depression: a meta-analysis. *J Nerv Ment Dis.* 2011;199(3):142-149.
229. van Hees ML, Rotter T, Ellermann T, Evers SM. The effectiveness of individual interpersonal psychotherapy as a treatment for major depressive disorder in adult outpatients: a systematic review. *BMC Psychiatry.* 2013;13:22.
230. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One.* 2010;5(10):e13196.
231. Griffiths KM, Farrer L, Christensen H. The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials. *Med J Aust.* 2010;192(11 Suppl):S4-11.
232. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev.* 2012;32(4):329-342.
233. So M, Yamaguchi S, Hashimoto S, Sado M, Furukawa TA, McCrone P. Is computerised CBT really helpful for adult depression?-A meta-analytic re-evaluation of CCBT for adult depression in terms of clinical implementation and methodological validity. *BMC Psychiatry.* 2013;13:113.
234. Jakobsen JC, Hansen JL, Simonsen E, Gluud C. The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. *J Affect Disord.* 2012;137(1-3):4-14.
235. Cuijpers P, van Straten A, Hollon SD, Andersson G. The contribution of active medication to combined treatments of psychotherapy and pharmacotherapy for adult depression: a meta-analysis. *Acta Psychiatr Scand.* 2010;121(6):415-423.
236. Cuijpers P, Andersson G, Donker T, van Straten A. Psychological treatment of depression: results of a series of meta-analyses. *Nord J Psychiatry.* 2011;65(6):354-364.

237. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF, 3rd. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry.* 2014;13(1):56-67.

238. Cuijpers P, Dekker J, Hollon SD, Andersson G. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis (Structured abstract). *J Clin Psychiatry.* 2009;70(9):1219-1229. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009109415/frame.html.

239. Spijker J, van Straten A, Bockting CL, Meeuwissen JA, van Balkom AJ. Psychotherapy, antidepressants, and their combination for chronic major depressive disorder: a systematic review. *Can J Psychiatry.* 2013;58(7):386-392.

240. Danielsson L, Noras AM, Waern M, Carlsson J. Exercise in the treatment of major depression: a systematic review grading the quality of evidence. *Physiother Theory Pract.* 2013;29(8):573-585.

241. Mura G, Moro MF, Patten SB, Carta MG. Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. *CNS Spectr.* 2014;19(6):496-508.

242. Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for depression: a systematic review and meta-analysis. *Depress Anxiety.* 2013;30(11):1068-1083.

243. Josefsson T, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. *Scand J Med Sci Sports.* 2014;24(2):259-272.

244. Silveira H, Moraes H, Oliveira N, Coutinho ES, Laks J, Deslandes A. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. *Neuropsychobiology.* 2013;67(2):61-68.

245. Bridle C, Spanjers K, Patel S, Atherton NM, Lamb SE. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry.* 2012;201(3):180-185.

246. Krogh J, Nordentoft M, Sterne JA, Lawlor DA. The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry.* 2011;72(4):529-538.

247. Woltmann E, Grogan-Kaylor A, Perron B, Georges H, Kilbourne AM, Bauer MS. Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: systematic review and meta-analysis. *Am J Psychiatry.* 2012;169(8):790-804.

248. Cuijpers P, van Straten A, Schuurmans J, van Oppen P, Hollon SD, Andersson G. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. *Clin Psychol Rev.* 2010;30(1):51-62.

249. Kriston L, von Wolff A, Westphal A, Holzel LP, Harter M. Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis. *Depress Anxiety.* 2014;31(8):621-630.

250. von Wolff A, Holzel LP, Westphal A, Harter M, Kriston L. Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis. *J Affect Disord.* 2013;144(1-2):7-15.

251. Krishna M, Honagodu A, Rajendra R, Sundarachar R, Lane S, Lepping P. A systematic review and meta-analysis of group psychotherapy for sub-clinical depression in older adults. *Int J Geriatr Psychiatry.* 2013;28(9):881-888.

252. Lee SY, Franchetti MK, Imanbayev A, Gallo JJ, Spira AP, Lee HB. Non-pharmacological prevention of major depression among community-dwelling older adults: a systematic review of the efficacy of psychotherapy interventions. *Arch Gerontol Geriatr.* 2012;55(3):522-529.
253. Cameron IM, Reid IC, MacGillivray SA. Efficacy and tolerability of antidepressants for sub-threshold depression and for mild major depressive disorder. *J Affect Disord.* 2014;166:48-58.
254. Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. *Psychiatry Res.* 2011;187(3):441-453.
255. Lopes Rocha F, Fuzikawa C, Riera R, Ramos MG, Hara C. Antidepressant combination for major depression in incomplete responders--a systematic review. *J Affect Disord.* 2013;144(1-2):1-6.
256. Feng CY, Chu H, Chen CH, et al. The effect of cognitive behavioral group therapy for depression: a meta-analysis 2000-2010. *Worldviews Evid Based Nurs.* 2012;9(1):2-17.
257. Glue P, Donovan MR, Kolluri S, Emir B. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. *Aust N Z J Psychiatry.* 2010;44(8):697-705.
258. Guidi J, Fava GA, Fava M, Papakostas GI. Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. *Psychol Med.* 2011;41(2):321-331.
259. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clin Psychol Rev.* 2011;31(6):1032-1040.
260. Zintzaras E, Miligkos M, Ziakas P, et al. Assessment of the relative effectiveness and tolerability of treatments of type 2 diabetes mellitus: a network meta-analysis. *Clin Ther.* 2014;36(10):1443-1453.e1449.
261. Guo X, Liu X, Wang M, Wei F, Zhang Y, Zhang Y. The effects of bariatric procedures versus medical therapy for obese patients with type 2 diabetes: meta-analysis of randomized controlled trials. *Biomed Res Int.* 2013;2013:410609.
262. Li JF, Lai DD, Ni B, Sun KX. Comparison of laparoscopic Roux-en-Y gastric bypass with laparoscopic sleeve gastrectomy for morbid obesity or type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Can J Surg.* 2013;56(6):E158-164.
263. Picot J, Jones J, Colquitt JL, Loveman E, Clegg AJ. Weight loss surgery for mild to moderate obesity: a systematic review and economic evaluation. *Obes Surg.* 2012;22(9):1496-1506.
264. Dixon JB, Murphy DK, Segel JE, Finkelstein EA. Impact of laparoscopic adjustable gastric banding on type 2 diabetes. *Obes Rev.* 2012;13(1):57-67.
265. Yip S, Plank LD, Murphy R. Gastric bypass and sleeve gastrectomy for type 2 diabetes: a systematic review and meta-analysis of outcomes. *Obes Surg.* 2013;23(12):1994-2003.
266. van Vugt M, de Wit M, Cleijne WH, Snoek FJ. Use of behavioral change techniques in web-based self-management programs for type 2 diabetes patients: systematic review. *J Med Internet Res.* 2013;15(12):e279.
267. Liang X, Wang Q, Yang X, et al. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. *Diabet Med.* 2011;28(4):455-463.
268. Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. *Diabetes Care.* 2011;34(5):1228-1237.

269. Schwingshackl L, Missbach B, Dias S, Konig J, Hoffmann G. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetologia.* 2014;57(9):1789-1797.
270. Vaes AW, Cheung A, Atakhorrami M, et al. Effect of 'activity monitor-based' counseling on physical activity and health-related outcomes in patients with chronic diseases: A systematic review and meta-analysis. *Ann Med.* 2013;45(5-6):397-412.
271. Hovanec N, Sawant A, Overend TJ, Petrella RJ, Vandervoort AA. Resistance training and older adults with type 2 diabetes mellitus: strength of the evidence. *J Aging Res.* 2012;2012:284635.
272. Lee MS, Jun JH, Lim HJ, Lim HS. A systematic review and meta-analysis of tai chi for treating type 2 diabetes. *Maturitas.* 2015;80(1):14-23.
273. MacLeod SF, Terada T, Chahal BS, Boule NG. Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using continuous glucose monitoring. *Diabetes Metab Res Rev.* 2013;29(8):593-603.
274. McGinley SK, Armstrong MJ, Boule NG, Sigal RJ. Effects of exercise training using resistance bands on glycaemic control and strength in type 2 diabetes mellitus: a meta-analysis of randomised controlled trials. *Acta Diabetol.* 2014.
275. Oliveira C, Simoes M, Carvalho J, Ribeiro J. Combined exercise for people with type 2 diabetes mellitus: a systematic review. *Diabetes Res Clin Pract.* 2012;98(2):187-198.
276. Umpierre D, Ribeiro PA, Schaan BD, Ribeiro JP. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. *Diabetologia.* 2013;56(2):242-251.
277. Yang Z, Scott CA, Mao C, Tang J, Farmer AJ. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. *Sports Med.* 2014;44(4):487-499.
278. Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. *Sports Med.* 2010;40(5):397-415.
279. Yan JH, Gu WJ, Pan L. Lack of evidence on Tai Chi-related effects in patients with type 2 diabetes mellitus: a meta-analysis. *Exp Clin Endocrinol Diabetes.* 2013;121(5):266-271.
280. Zhou J, Zhang L, Liu H, Mallampati T, Xu M, Yang J. Tai Chi for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2012(3). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009717/abstract.
281. Castaneda-Gonzalez LM, Bacardi Gascon M, Jimenez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. *Nutr Hosp.* 2011;26(6):1270-1276.
282. Dong JY, Zhang ZL, Wang PY, Qin LQ. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. *Br J Nutr.* 2013;110(5):781-789.
283. Schwingshackl L, Hoffmann G. Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis. *Br J Nutr.* 2014;111(12):2047-2058.
284. Ricci-Cabello I, Ruiz-Perez I, Rojas-Garcia A, Pastor G, Goncalves DC. Improving diabetes care in rural areas: a systematic review and meta-analysis of quality improvement interventions in OECD countries. *PLoS One.* 2013;8(12):e84464.

285. Searle A, Spink M, Ho A, Chuter V. Exercise interventions for the treatment of chronic low back pain: A systematic review and meta-analysis of randomised controlled trials. *Clin Rehabil.* 2015.
286. Wang XQ, Zheng JJ, Yu ZW, et al. A meta-analysis of core stability exercise versus general exercise for chronic low back pain. *PLoS One.* 2012;7(12):e52082.
287. Schaafsma FG, Whelan K, van der Beek AJ, van der Es-Lambeek LC, Ojajarvi A, Verbeek JH. Physical conditioning as part of a return to work strategy to reduce sickness absence for workers with back pain. *Cochrane Database Syst Rev.* 2013;8:Cd001822.
288. Ferreira ML, Smeets RJ, Kamper SJ, Ferreira PH, Machado LA. Can we explain heterogeneity among randomized clinical trials of exercise for chronic back pain? A meta-regression analysis of randomized controlled trials. *Phys Ther.* 2010;90(10):1383-1403.
289. Fersum KV, Dankaerts W, O'Sullivan PB, et al. Integration of subclassification strategies in randomised controlled clinical trials evaluating manual therapy treatment and exercise therapy for non-specific chronic low back pain: a systematic review. *Br J Sports Med.* 2010;44(14):1054-1062.
290. Miyamoto GC, Costa LO, Cabral CM. Efficacy of the Pilates method for pain and disability in patients with chronic nonspecific low back pain: a systematic review with meta-analysis. *Braz J Phys Ther.* 2013;17(6):517-532.
291. Pereira LM, Obara K, Dias JM, et al. Comparing the Pilates method with no exercise or lumbar stabilization for pain and functionality in patients with chronic low back pain: systematic review and meta-analysis. *Clin Rehabil.* 2012;26(1):10-20.
292. Standaert CJ, Friedly J, Erwin MW, et al. Comparative effectiveness of exercise, acupuncture, and spinal manipulation for low back pain. *Spine (Phila Pa 1976).* 2011;36(21 Suppl):S120-130.
293. Orrock PJ, Myers SP. Osteopathic intervention in chronic non-specific low back pain: a systematic review. *BMC Musculoskelet Disord.* 2013;14:129.
294. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. *Cochrane Database Syst Rev.* 2011(2):Cd008112.
295. Rubinstein SM, van Middelkoop M, Kuijpers T, et al. A systematic review on the effectiveness of complementary and alternative medicine for chronic non-specific low-back pain. *Eur Spine J.* 2010;19(8):1213-1228.
296. Xu M, Yan S, Yin X, et al. Acupuncture for chronic low back pain in long-term follow-up: a meta-analysis of 13 randomized controlled trials. *Am J Chin Med.* 2013;41(1):1-19.
297. Falco FJ, Manchikanti L, Datta S, et al. An update of the effectiveness of therapeutic lumbar facet joint interventions. *Pain Physician.* 2012;15(6):E909-953.
298. Parr AT, Manchikanti L, Hameed H, et al. Caudal epidural injections in the management of chronic low back pain: a systematic appraisal of the literature. *Pain Physician.* 2012;15(3):E159-198.
299. Chou R, Baisden J, Carragee EJ, Resnick DK, Shaffer WO, Loeser JD. Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline. *Spine (Phila Pa 1976).* 2009;34(10):1094-1109.
300. van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J.* 2011;20(1):19-39.

301. Clarke CL, Ryan CG, Martin DJ. Pain neurophysiology education for the management of individuals with chronic low back pain: systematic review and meta-analysis. *Man Ther.* 2011;16(6):544-549.

302. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2014;4:Cd007938.

303. Boyers D, McNamee P, Clarke A, et al. Cost-effectiveness of self-management methods for the treatment of chronic pain in an aging adult population: a systematic review of the literature. *Clin J Pain.* 2013;29(4):366-375.

304. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Available at: http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Western-Ontario-McMaster-Universities-Osteoarthritis-Index-WOMAC. Accessed September 16, 2015.

APPENDIX A. CONDITION PRIORITIZATION INSTRUCTIONS

Please prioritize the list of health conditions by assigning 0 to 3 stars to items listed below. When prioritizing, consider the following: (1) prevalence of the condition in Veterans, (2) the burden of the illness, (3) priorities for gender-specific care for women Veterans (not Active Duty), and (4) conditions with known disparities between women Veterans and non-Veterans. Items are categorized by conditions affecting men and women compared with gender-specific conditions.

You are given a **total of 11 stars** to allocate to any of the **34 items listed** in the 2 categories. You may use up to **3 stars per item**. To add stars to a selection, position your mouse over the dots in the right hand column. More stars equal higher priority.

Alzheimer's disease
Anxiety (*ie*, GAD, panic disorder)
Osteoporosis
Coronary artery disease (*ie*, chronic angina)
Coronary artery disease (*ie*, acute coronary syndrome/myocardial infarction)
Chronic obstructive pulmonary disease
Cerebrovascular disease (*ie*, ischemic stroke)
Depression (*ie*, MDD & dysthymia)
Diabetes mellitus-type2
Eating disorders
Connective tissue disease (*ie*, fibromyalgia)
Headache (*ie*, migraine)
Hepatitis-C
HIV
Hyperlipidemia
Hypertension
Irritable bowel syndrome
Incontinence
Insomnia
Joint disorders (*ie*, osteoarthritis: hip and knee)
Joint disorders (*ie*, rheumatoid arthritis)
Obesity/overweight
Chronic pain
Posttraumatic stress disorder
Spine disorders (*ie*, chronic low back pain)
Substance use disorder
Traumatic brain injury
Thyroid disorders
Tobacco use disorder

SEPARATOR BETWEEN SEX-SPECIFIC ITEMS
Contraceptive care
Infertility
Menstrual disorders (*ie*, abnormal uterine bleeding)
Menopausal disorders
Depressive disorders (*ie*, postpartum depression)
Depressive disorders (*ie*, premenstrual dysphoric disorder)
Prenatal care

APPENDIX B. SEARCH STRATEGIES

CONDITION: MAJOR DEPRESSIVE DISORDER

PubMed: Searched October 31, 2014

Search	Query	Items found
#1	Search "Depressive Disorder"[Mesh:NoExp] OR "Depressive Disorder, Major"[MeSH] OR "major depressive disorder"[tiab] OR "major depressive disorders"[tiab] OR "major depression"[tiab] OR “Involutional Psychoses”[tiab] OR “Involutional Psychosis”[tiab] OR “Involutional Depression”[tiab] OR “Involutional Melancholia”[tiab] OR "Dysthymic Disorder"[Mesh] OR "Dysthymic Disorder"[tiab] OR "Dysthymic Disorders"[tiab] OR “dysthymia”[tiab]	87024
#2	Search “Psychotherapy”[Mesh] OR “Behavior Therapy”[Mesh] OR acceptance therap*[tiab] OR commitment therap*[tiab] OR cognitive therap*[tiab] OR behavioral therap*[tiab] OR behavior therap*[tiab] OR behaviour therap*[tiab] OR behavioural therap*[tiab]OR interpersonal therap*[tiab] OR acceptance therap*[tiab] OR commitment therap*[tiab] OR mindfulness therap*[tiab] OR problem-solving therap*[tiab] OR problem solving therap*[tiab] OR psychodynamic therap*[tiab] OR psychotherap*[tiab]	172225
#3	Search "antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR "antidepressive"[tiab] OR antidepressant*[tiab]	141775
#4	Search “Delivery of Health Care, Integrated”[Mesh] OR “Patient Care Team”[Mesh] OR “Patient Care Planning”[Mesh] OR “Disease Management”[Mesh] OR “Comprehensive Health Care” [Mesh:noexp] OR “Patient Care Management”[Mesh:noexp] OR “coordinated care”[tiab] OR coordinated program*[tiab] OR “team care”[tiab] OR “team treatment”[tiab] OR “team assessment”[tiab] OR “team consultation”[tiab] OR (collaborat*[ti] AND care [ti]) OR “shared care”[tiab] OR (collaborat*[ti] AND manage*[ti]) OR “Quality Improvement”[Mesh]	154585
#5	("Exercise"[Mesh:NoExp] OR "Exercise"[Majr] OR "Circuit-Based Exercise"[Mesh] OR "Muscle Stretching Exercises"[Mesh] OR "Physical Conditioning, Human"[Mesh] OR "Resistance Training"[Mesh] OR "Resistance Training"[tiab] OR "Exercise"[tiab] OR "Exercises"[tiab] OR "physical activity"[tiab] OR "aerobic activity"[tiab] OR "Exercise Movement Techniques"[Mesh] OR "Sports"[Mesh] OR "yoga"[tiab] OR "Exercise Therapy"[Mesh]	
#5	Search #1 AND (#2 OR #3 OR #4 OR #5)	32393
#6	Search #5 AND (systematic[sb] OR "Systematic Review"[tiab] OR meta-analysis[tiab] OR "meta analysis"[tiab])	1792
#7	Search #6 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh])	1677
#8	Search #7 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	1677
#9	Search #7 NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) Filters: published in the last 5 years	631
#10	Search #7 NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) Sort by: Author Filters: published in the last 5 years; English	581

Cochrane Library: Searched October 31, 2014

ID	Search	Results
#1	major depressive disorder:ti,ab,kw (Word variations have been searched)	2783

ID	Search	Results
#2	major depression:ti,ab,kw (Word variations have been searched)	3691
#3	major depression disorder:ti,ab,kw (Word variations have been searched)	24
#4	dysthymic disorder:ti,ab,kw (Word variations have been searched)	241
#5	dysthymia:ti,ab,kw (Word variations have been searched)	379
#6	involutional depression:ti,ab,kw (Word variations have been searched)	12
#7	involutional melancholia:ti,ab,kw (Word variations have been searched)	0
#8	involutional psychosis:ti,ab,kw (Word variations have been searched)	0
#9	involutional psychoses:ti,ab,kw (Word variations have been searched)	0
#10	(or #1-#9)	6077
#11	#10 Publication Year from 2009 to 2014, in Cochrane Reviews (Reviews only) and Other Reviews	117

CONDITION: TYPE 2 DIABETES

PubMed: Searched February 6, 2015

Search	Query	Items found
#1	Search "Diabetes Mellitus, Type 2"[Mesh] OR "Type 2 Diabetes Mellitus"[tiab] OR "Type II Diabetes Mellitus"[tiab] OR "Adult-Onset Diabetes Mellitus"[tiab] OR "Adult Onset Diabetes Mellitus"[tiab] OR "Maturity-Onset Diabetes Mellitus"[tiab] OR "Maturity Onset Diabetes Mellitus"[tiab] OR "Non-Insulin-Dependent Diabetes Mellitus"[tiab] OR "Non-Insulin Dependent Diabetes Mellitus"[tiab] OR "Noninsulin Dependent Diabetes Mellitus"[tiab] OR "Ketosis-Resistant Diabetes Mellitus"[tiab] OR "Ketosis Resistant Diabetes Mellitus"[tiab] OR "Stable Diabetes Mellitus"[tiab]	97698
#2	Search "Hypoglycemic Agents"[Mesh] OR "Hypoglycemic Agents"[Pharmacological Action] OR "Metformin"[Mesh] OR "Metformin"[tiab] OR "Glyburide"[Mesh] OR "Glyburide"[tiab] OR "Glipizide"[Mesh] OR "Glipizide"[tiab] OR "glibenclamide receptor"[Supplementary Concept] OR "glibenclamide"[tiab] OR "Gliclazide"[Mesh] OR "Gliclazide"[tiab] OR "glimepiride"[Supplementary Concept] OR "glimepiride"[tiab] OR "repaglinide"[Supplementary Concept] OR "repaglinide"[tiab] OR "nateglinide"[Supplementary Concept] OR "nateglinide"[tiab] OR "pioglitazone"[Supplementary Concept] OR "pioglitazone"[tiab] OR "rosiglitazone"[Supplementary Concept] OR "rosiglitazone"[tiab] OR "Acarbose"[Mesh] OR "Acarbose"[tiab] OR "miglitol" [Supplementary Concept] OR "miglitol"[tiab] OR "sitagliptin"[Supplementary Concept] OR "sitagliptin"[tiab] OR "vildagliptin"[Supplementary Concept] OR "vildagliptin"[tiab] OR "saxagliptin"[Supplementary Concept] OR "saxagliptin"[tiab] OR "Linagliptin"[Supplementary Concept] OR "Linagliptin"[tiab] OR "alogliptin"[Supplementary Concept] OR "alogliptin"[tiab] OR "colesevelam"[Supplementary Concept] OR "colesevelam"[tiab] OR "Bromocriptine"[Mesh] OR "Bromocriptine"[tiab] OR "canagliflozin"[Supplementary Concept] OR "canagliflozin"[tiab] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"[Supplementary Concept] OR "dapagliflozin"[tiab] OR "empagliflozin"[Supplementary Concept] OR "empagliflozin"[tiab] OR "exenatide"[Supplementary Concept] OR "exenatide"[tiab] OR "liraglutide"[Supplementary Concept] OR "liraglutide"[tiab] OR "albiglutide"[Supplementary Concept] OR "albiglutide"[tiab] OR "ZP10A peptide"[Supplementary Concept] OR "Lixisenatide"[tiab] OR "dulaglutide"[Supplementary Concept] OR "dulaglutide"[tiab] OR "pramlintide"[Supplementary Concept] OR "pramlintide"[tiab]	220517

Search	Query	Items found
#3	Search #1 AND #2	31000
#4	Search "Insulins"[Mesh] OR "Lispro"[tiab] OR "Aspart"[tiab] OR "insulin glulisine"[Supplementary Concept] OR "glulisine"[tiab] OR "isophane insulin, human"[Supplementary Concept] OR "glargine"[Supplementary Concept] OR "glargine"[tiab] OR "insulin detemir"[Supplementary Concept] OR "detemir"[tiab] OR "insulin degludec"[Supplementary Concept] OR "degludec"[tiab]	162510
#5	Search #1 AND #4	18805
#6	Search "Exercise"[Mesh] OR "Exercise"[tiab] OR "Exercise Therapy"[Mesh] OR "physical activity"[tiab]	296513
#7	Search #1 AND #6	6871
#8	Search "Weight Reduction Programs"[Mesh] OR "Weight Reduction Program"[tiab] OR "Weight control Program"[tiab] OR "Nutrition Therapy"[Mesh] OR "weight management"[tiab]	83630
#9	Search #1 AND #8	2694
#10	Search "Bariatric Surgery"[Mesh] OR "Bariatric Surgery"[tiab]	17552
#11	Search #1 AND #10	1329
#12	Search "Patient Care Management"[Mesh] OR "multidisciplinary care"[tiab] OR "shared medical appointments"[tiab] OR "chronic disease management"[tiab] OR "stepped-care models"[tiab] OR "stepped-care model"[tiab] OR "stepped care models"[tiab] OR "stepped care model"[tiab] OR (nurse managed clinic[tiab] OR nurse managed clinics[tiab]) OR (nurse managed clinic[tiab] OR nurse managed clinics[tiab]) OR "Cell Phones"[Mesh] OR "smartphone applications"[tiab] OR "Quality Improvement"[Mesh]	554128
#13	Search #1 AND #12	3965
#14	Search #3 OR #5 OR #7 OR #9 OR #11 OR #13	41293
#15	Search #14 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])	40423
#16	Search #15 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	37107
#17	Search #16 AND (systematic[sb] OR "Systematic Review"[tiab] OR "Umbrella Review"[tiab] OR meta-analysis[tiab] OR "meta analysis"[tiab]) AND "English"[lang]	1442

CONDITION: CHRONIC PAIN

PubMed: Searched February 27, 2015

Search	Query	Items found
#1	Search "chronic pain"[MeSH Terms] OR "chronic pain"[tiab] OR "chronic pains"[tiab] OR "Fibromyalgia"[Mesh] OR "Fibromyalgia"[tiab] OR "Fibromyalgias"[tiab] OR "Muscular Rheumatism"[tiab] OR "Fibrositis"[tiab] OR "Pain Syndrome"[tiab] OR "chronic low back pain"[tiab] OR "chronic knee pain"[tiab] OR “knee osteoarthritis”[MeSH Terms] OR “knee osteoarthritis”[tiab]	41472
#2	Search #1 AND (systematic[sb] OR "Systematic Review"[tiab] OR "Umbrella Review"[tiab] OR meta-analysis[tiab] OR "meta analysis"[tiab]) AND "English"[lang]	2031
#3	Search #2 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	2025
#4	Search #3 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh])	1985
#5	Search (("2009/10/01"[Date - Publication] : "3000"[Date - Publication])) AND #4	1145
#6	Search #5 AND ("Behavior Therapy"[Mesh] OR "psychoeducation"[tiab] OR "CBT"[tiab] OR "biofeedback"[tiab] OR (("therapy"[tiab]) AND ("mindfulness"[tiab]	92

Search	Query	Items found
	OR "cognitive"[tiab] OR "behavior"[tiab] OR "behavioral"[tiab] OR "relaxation"[tiab] OR "acceptance"[tiab])))	
#7	Search #5 AND ("Exercise"[Mesh:NoExp] OR "Exercise"[Majr] OR "Circuit-Based Exercise"[Mesh] OR "Muscle Stretching Exercises"[Mesh] OR "Physical Conditioning, Human"[Mesh] OR "Resistance Training"[Mesh] OR "Resistance Training"[tiab] OR "Running"[Mesh] OR "Running"[tiab] OR "Jogging"[Mesh] OR "Jogging"[tiab] OR "Swimming"[Mesh] OR "Swimming"[tiab] OR "Walking"[Mesh] OR "Walking"[tiab] OR "Exercise"[tiab] OR "Exercises"[tiab] OR "physical activity"[tiab] OR "aerobic activity"[tiab] OR "Exercise Movement Techniques"[Mesh] OR "Sports"[Mesh] OR "yoga"[tiab] OR "Physical Therapy Modalities"[Mesh:NoExp] OR "Physical Therapy"[tiab] OR "Exercise Therapy"[Mesh] OR "Hydrotherapy"[Mesh] OR "Hydrotherapy"[tiab])	**196**
#8	Search #5 AND ("Muscle Relaxants, Central"[Mesh] OR "Baclofen"[Mesh] OR "Baclofen"[tiab] OR "Carisoprodol"[Mesh] OR "Carisoprodol"[tiab] OR "cyclobenzaprine" [Supplementary Concept] OR "cyclobenzaprine"[tiab] OR "Methocarbamol"[Mesh] OR "Methocarbamol"[tiab] OR "tizanidine"[Supplementary Concept] OR "tizanidine"[tiab])	**2**
#9	Search #5 AND ("Anti-Inflammatory Agents, Non-Steroidal" [Pharmacological Action] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "NSAIDs"[tiab] OR "Nonsteroidal Anti Inflammatory Agents"[tiab] OR "Nonsteroidal Anti Inflammatory Agent"[tiab])	**41**
#10	Search #5 AND ("Capsaicin"[Mesh] OR "Capsaicin"[tiab])	**10**
#11	Search #5 AND (("Lidocaine"[MeSH Terms] OR "lidocaine"[tiab]) AND ("transdermal patch"[MeSH Terms] OR "transdermal"[tiab] OR "patch"[tiab]))	**1**
#12	Search #5 AND ("Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Duloxetine"[tiab] OR "Venlafaxine"[tiab])	**60**
#13	Search #5 AND ("pregabalin" [Supplementary Concept] OR "pregabalin" [tiab])	**38**
#14	Search #5 AND ("gabapentin" [Supplementary Concept] OR "gabapentin" [tiab])	**23**
#15	Search #5 AND ("Hyaluronic Acid"[Mesh] OR "Hyaluronic Acid"[tiab])	**4**
#16	Search #5 AND ("Steroids"[Mesh] OR "steroid"[tiab] OR "steroids"[tiab])	**28**
#17	Search #5 AND ("Acupuncture Therapy"[Mesh] OR "Acupuncture"[Mesh] OR "Acupuncture"[tiab] OR "Chiropractic"[Mesh] OR "Manipulation, Chiropractic"[Mesh] OR "Chiropractic"[tiab] OR "Chiropractor"[tiab])	**58**
#18	Search #5 AND ("Patient Care Management"[Mesh] OR "multidisciplinary care"[tiab] OR "colocated care"[tiab] OR "shared medical appointments"[tiab] OR "pain clinic"[tiab] OR "Telephone"[MAJR] OR "Cell Phones"[Mesh] OR "smartphone applications"[tiab] OR "telephone-based care"[tiab] OR "telephone care"[tiab] OR "Quality Improvement"[Mesh] OR "Continuity of Patient Care"[Mesh] OR "Patient-Centered Care"[Mesh] OR "chronic disease management"[tiab])	**196**
#19	Search #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	**538**

Cochrane Library: Searched February 27, 2015

ID	Search	Results
#1	"chronic pain":ti,ab,kw (Word variations have been searched)	**2689**
#2	"fibromyalgia":ti,ab,kw (Word variations have been searched)	**1249**
#3	#1 or #2 Publication Year from 2009 to 2015, in Cochrane Reviews (Reviews and Protocols)	**88**

APPENDIX C. ELIGIBILITY CRITERIA FOR SYSTEMATIC REVIEWS

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	**Depressive disorders:** Adults with major depressive disorder, persistent depressive disorder (dysthymia), or subsyndromal depression/minor depression/depression-NOS; also included are reviews broadly addressing effects of treatment in patients with co-occurring chronic medial illness **Diabetes:** Adults with type 2 diabetes mellitus[a] **Chronic pain:** Adults with musculoskeletal causes of chronic low back pain, fibromyalgia, or chronic knee pain due to osteoarthritis	**Depressive disorders:** Reviews focused on bipolar disorder, grief, premenstrual dysphoric disorder, psychotic depression, depression subtypes (*eg*, atypical depression; melancholic depression); also excluded are reviews focused on subsets of depressed patients who have a specific comorbid medical condition (*eg*, diabetes, heart disease) or psychiatric illness (*eg*, alcohol misuse) **Diabetes:** None **Chronic pain:** Reviews focused only on acute back or knee pain, other pain syndromes (*eg*, patellofemoral)
Interventions	**Depressive disorders**[b]: · Antidepressants (SSRI, SNRI, TCA) · Therapy: CBT, CT, IPT, MBCT, PST, ST, psychodynamic, reminiscence therapy delivered in person, in groups, or by internet · Supervised exercise · Guided self-help based on principles of CBT · QI strategies: collaborative care, co-located care, women-only clinic **Diabetes:** · Oral hypoglycemics: metformin, DPP-4 inhibitors (*eg*, saxagliptin), sulfonylureas (*eg*, glipizide, glyburide), GLP-1 inhibitors (*eg*, exanatide, liraglutide), thiazolidenediones (*eg* pioglitazone) · Insulin · Exercise programs: aerobic or strengthening performed in organized groups or with support from behaviorist[c] · Behavioral: psychoeducation, weight control program[d] · Bariatric surgery · QI strategies: multidisciplinary care (*eg*, co-located behaviorist, registered dietician, or diabetic educator),	**Depressive disorders:** · Alternative: dietary supplements (*eg*, fish oil; vitamin D), yoga, acupuncture, St. John's wort, SAM-e · Medications: atypical antipsychotics, ketamine, adjunctive medications used for augmentation (*eg*, psychostimulants, thyroid hormone, lithium) that have not been specified as eligible medications; reviews of single medications, rather than a drug class, unless review is an individual patient data meta-analysis · Somatic: electroconvulsive therapy, light therapy, transcranial magnetic stimulation, vagal nerve stimulation, deep brain stimulation · Psychotherapies: dialectical behavioral therapy, music therapy, traditional long-term psychodynamic therapy, pet therapy · Treatment sequencing (*eg*, switching antidepressants) · Interventions to prevent depressive disorder (*eg*, interferon therapy for hepatitis C) **Diabetes:** · Interventions to prevent diabetes · Alternative: dietary supplements, acupuncture, meditation-based interventions (*eg*, transcendental meditation)

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	shared medical appointments, chronic disease management (*eg*, telephone and internet-based interventions), stepped-care models, nurse-managed clinics, women-only clinic, smartphone applications **Chronic pain:** · Antidepressants: SNRIs (duloxetine, venlafaxine, milnacipran), TCA, SSRI · Calcium channel 2 delta ligands[e]: pregabalin, gabapentin · Muscle relaxants[e] · Topical treatments: NSAIDs, capsaicin, lidocaine patch · Joint injection: steroid (if back, must be lumbar region)[f], hyaluronic acid[g] · Behavioral treatments focused on pain management: psychoeducation, CBT, mindfulness-based and acceptance-based therapy, relaxation therapy, biofeedback in groups or by internet · Exercise: aerobic, strengthening, or stretching performed with supervision (*eg*, physical therapist, pool therapy), as part of a class (*eg*, yoga class, tai chi), or as medically directed self-care · Integrative and complementary medicine[e]: acupuncture; spinal manipulation (chiropractic care) · QI strategies: multidisciplinary care (*eg*, multidisciplinary pain clinic), co-located care (*eg*, behaviorist in primary care), women-only clinic; telephone-based care · Self-management strategies used to decrease pain symptoms	· Medications: any medication or class of medication not listed in the included section, insulin pump regimens, types or intensity of insulin regimens, colesevalam, alpha-glucosidase inhibitors, bromocriptine, miglitol; reviews of single medications unless the medication is insulin, metformin, repaglinide, nateglinide, pioglitazone, rosiglitazone, or pramlintide, or review is an individual patient data meta-analysis · Somatic: type or intensity of glucose monitoring · Surgical interventions other than bariatric surgery · QI: endocrinology clinics, QI interventions with clinician as intervention target (*eg*, decision support via computer reminders) **Chronic pain:** · Complementary and integrative medicine: massage, dietary supplements · Medications: acetaminophen, oral NSAIDs, antiepileptics (except for gabapentin, pregabalin); antispasmodics; antipsychotics, clozapine, benzodiazepine and opioids; reviews of single medications except: amitriptyline, pregabalin, gabapentin, duloxetine, milnacipran, capsaicin, lidocaine, or review is an individual patient data meta-analysis · Marijuana/cannabinoids · Injections/physical: nerve blocks, therapeutic ultrasound, traction, back braces, knee braces, TENS unit, trigger point injections · Surgical interventions (*eg*, spinal fusion; total hip or total knee arthroplasty, spinal cord stimulator) · Therapies: dialectical behavioral therapy, music therapy, traditional long-term psychodynamic therapy, pet therapy · Treatment sequencing (*eg*, acetaminophen then NSAID) · Interventions to prevent chronic pain
Comparators	All conditions: Any active or inactive comparators	None

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Outcomes	All conditions: Patient health outcomes and adverse effects · **Depressive disorders:** Depressive symptoms, functional status · **Diabetes:** Glycemic control, weight, mortality, microvascular and macrovascular events[h], adverse effects[i] · **Chronic pain:** Pain severity, functional status	**Depressive disorders:** Provider outcomes, acceptance of intervention, prevalence of intervention, cost of intervention without reporting patient health outcomes **Diabetes:** Provider outcomes, adherence to and/or acceptance of intervention, blood pressure, lipids, prevalence of intervention, cost of intervention **Chronic pain:** Provider outcomes, adherence to and/or acceptance of intervention, prevalence of intervention; cost of intervention without reporting patient health outcomes
Timing	Any duration of follow-up	None
Settings	**Depressive disorders:** Any setting **Diabetes:** Outpatient settings **Chronic pain:** Outpatient settings	**Depressive disorders**: None **Diabetes:** In-hospital setting, or focused on effects in low-income countries **Chronic pain:** Focused on work-based programs
Design	All conditions: Systematic reviews or individual patient level meta-analyses; must have search strategy, eligibility criteria, and analysis/synthesis plan · **Depressive disorders:** May include RCTs (antidepressants, therapy, exercise), or quasi-experimental studies (QI interventions), or observational studies (if focused on adverse effects) · **Diabetes:** May include RCTs (medications, behavioral interventions), or quasi-experimental studies (QI interventions), or observational studies (if focused on adverse effects) · **Chronic pain:** May include RCTs (medications, behavioral, exercise), or quasi-experimental studies (QI strategies), or observational studies (if focused on adverse effects)	Nonsystematic reviews
Publications	English-language only	Non-English publications

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	Published October 2009 to present	Publications before October 2009

[a] Mixed diabetes populations were included if patients with type 2 diabetes were analyzed separately.
[b] Interventions may be for acute-phase treatment, treatment-resistant depression, or maintenance.
[c] Includes tai chi, Pilates, yoga, and related forms of exercise.
[d] Includes supervised programs that use changes in physical activity, diet, or a combination of these approaches to achieve weight change or improved glycemic control.
[e] For chronic low back pain and fibromyalgia only.
[f] For chronic low back pain and chronic knee pain only.
[g] For chronic knee pain only.
[h] Includes stroke, cardiac event (*eg*, myocardial infarction), nephropathy, neuropathy (including diabetic foot ulcer), and changes in cognition.
[I] Includes cancer, osteoporosis, hypoglycemia, changes in cognition, lactic acidosis, adverse gastrointestinal effects, and cardiovascular and serious adverse events.
Abbreviations: CBT=cognitive behavioral therapy; CT=cognitive therapy; DPP-4=dipeptidyl peptidase 4; GLP-1=glucagon-like peptide-1; IPT=interpersonal therapy; MBCT=mindfulness-based cognitive therapy; NOS=not otherwise specified; NSAID=nonsteroidal anti-inflammatory drug; PICOTS=population, intervention, comparator, outcome, timing, setting; PST=problem-solving therapy; QI=quality improvement; RCT=randomized controlled trial; SAM-e=S-adenosylmethionine; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; ST psychodynamic=short-term psychodynamic; TCA=tricyclic antidepressant; TENS= transcutaneous electrical nerve stimulation

APPENDIX D. RESPONSES TO REVIEWER COMMENTS

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

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	Acknowledged
	3	Yes	Acknowledged
	4	Yes	Acknowledged
	5	Yes	Acknowledged
	7	Yes	Acknowledged
	8	Yes	Acknowledged
Is there any indication of bias in our synthesis of the evidence?	1	No	Acknowledged
	3	No	Acknowledged
	4	No	Acknowledged
	5	No	Acknowledged
	7	No	Acknowledged
	8	No	Acknowledged
Are there any published or unpublished studies that we may have overlooked?	1	No	Acknowledged
	3	No	Acknowledged
	4	Yes - It is difficult to know whether studies were overlooked, give the way results are reported in broad categories, but the evidence reviewed does not appear to be comprehensive or include the most high impact/high quality reviews available. For example, only one review of medications for low back pain is discussed (on page 22, citation 193). Other reviews of medications for back pain are available and seemingly should be included, but I can't tell if they were because the number of reviews of medications is presented for all chronic pain conditions combined. For LBP injections, 2 reviews from low tier journals are highlighted, but the high quality American Pain Society sponsored reviews of interventional therapies by Roger Chou et al (published in Journal of Pain in 2009) are not included.	We identified 3 Chou citations in the *Journal of Pain* during 2009. These were examined and found not eligible. However, we identified another review from this author in *Spine* (2009), which has been included in the final report. We also conducted a supplemental search for studies that addressed eligible interventions for chronic knee pain due to osteoarthritis. Additional eligible reviews were identified and are included in the final report. We think the relatively low number of eligible articles for chronic pain conditions is in part due to the interventions chosen for evaluation.

Question Text	Reviewer Number	Comment	Response
	5	No	Acknowledged
	7	No	Acknowledged
	8	No	Acknowledged
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft	1	Methodology seems very sound - further examination of primary trials is valuable and a good plan.	Thank you.
	3	Overall feedback: This review seeks to create "…an evidence map to aid prioritization and development of implementation projects and research initiatives" in order to address the emerging healthcare needs of women Veterans, which has the potential to be of great benefit to policy makers and researchers alike. Overall the manuscript flows exceedingly well and the authors present the information in a balanced, logical, thoughtful, and succinct manner. Particular strengths are the inclusiveness of the treatments types that were reviewed and the consistent organization and framing that facilitates readership from section to section. Overall this reviewer found that the manuscript may be enhanced by some minor adjustments or additions in the following specific areas: 1. The title, "Women's Health Evidence Map", is rather broadly worded given that the paper focuses on three health conditions (depression, DM, and chronic pain). This reviewer recommends re-working the title or adding a subtitle that speaks to the content area covered in the report. A subtitle may be particularly suitable if subsequent papers may expand the health evidence map by reviewing additional health conditions. 2. In various locations the studies contained within are referred to descriptively as "low grade", "low quality", "high quality", "good quality" and so forth. There is a paragraph within the paper that indicates that a formal	Thank you. We agree that the title was incomplete. It has been revised to "Mapping the Evidence: Sex Effects in High-impact Conditions for Women Veterans—Depression, Diabetes, and Chronic Pain." We've standardized the descriptors and clarified when we are referring to a high-quality review (as defined by a Cochrane, ESP, or EPC review) versus a summary statement about the quality of the evidence made by the

Question Text	Reviewer Number	Comment	Response
		assessment of methodological rigor is "beyond the scope of the project" (see Quality Assessment page 5) however subsequent use of these descriptors suggests at least informal evaluation of the papers. This reviewer suggests including a description (perhaps in the Quality Assessment section) that at least informally anchors these descriptors. In addition, would recommend standardizing the descriptors—*eg*, using low quality or low grade unless these two descriptors differ from one another. 3. The description of the iterative process and use of stakeholders to determine the health conditions chosen left this reviewer looking for additional information. For example, what was the composition of the stakeholder group? Why only three conditions versus some other number? Did the iterative process yield agreement/ranking that only suggested review of 3 health conditions with a fourth (or fifth, etc.,) not reaching a reasonable consensus or convergence of opinion? 4. Diabetes Section: page 16 the follow sentence may be improved by revising "last" to "lastly": "Last, all 3 reviews of DPP-4 inhibitors applied IPD meta-analyses to data from industry studies.137,142,143. " 5. Evidence Gaps for Sex Effects Subsection: The paragraph that starts "In response to underrepresentation of women and minorities…" while containing important information, seems out of place in a summary of the evidence gaps for sex effects and more suited to the subsequent section entitled "Achieving Adequate Representation of Women in Clinical Studies". The paragraph on "evidence gaps" may be enhanced by further description of where sex effects lead to reasonably sound information (information of use clinically) or to highlight what guidance is lacking with regard to clinical care given the very limited information regarding sex effects.	review authors. We've added additional detail to the methods to describe the stakeholders and the process for prioritizing the included conditions. Edit made. We have moved this paragraph to the recommended section. We considered the suggestion to add recommendations for clinical care. First, our goal was more descriptive. We also did not conduct a quality assessment of the systematic reviews. Furthermore, the sex results were generally small and arrived at by poorly suited analytic techniques. Thus, we do not feel confident in making specific clinical treatment recommendations. However, in order to address the clinical implications of our results, we have identified promising areas that could, with further research, lead to sex-specific clinical recommendations. In addition, we offer some discussion of how these proposed

Question Text	Reviewer Number	Comment	Response
			areas of research would impact clinical care for women.
		6. Achieving Adequate Representation of Women in Clinical Studies Subsection: It seems implicit in this paragraph that inclusion of women Veterans in research studies is somehow only available for women Veterans who are enrolled in VA care (i.e, the sentence on page 27 reads: "Inclusion of women in VA research is particularly challenging because the enrollment of women Veterans in VHA, while growing, remains a relatively low proportion (6.5% in 2012).". One could argue that adequate representation is also hampered by only enrolling women in VA care (into studies) rather that expanding recruitment to women Veterans more broadly. In addition, adequate representation of the needs of women Veterans more broadly is also affected by only studying only/primarily women enrolled in VA care. This portion of the paper may be improved by acknowledgement of these limitations and how these limitations may affect or influence the knowledge base.	We addressed this suggestion by broadening our discussion regarding barriers to recruitment, so that we noted (1) the small proportion of total veteran population who are women and (2) general barriers found for study participation by minorities and women. Thus, while we agree that expanding to women Veterans not enrolled in VA may increase the participant pool somewhat, we think this would ultimately not make a substantial difference. Additionally, recruiting these women poses significant complications for VA-based research, given that such projects often utilize VHA resources (*eg*, EHR).
		7. Prioritizing Areas for Evaluation of Sex Effects Subsection: most of this paragraph appears to speak to the prior sub-section content, which is Achieving Adequate Representation of Women in Clinical Studies. This reviewer suggests relocating this information to the above section and adding additional text in the Prioritizing Areas for Evaluation of Sex Effects that that includes suggestions that speak to the three content areas (depression, diabetes, chronic pain) that were so thoroughly reviewed in earlier portions of the paper.	Thank you for this comment. We've revised and expanded this section to include examples specific to conditions evaluated in the report.
		8. The paper would benefit from additional discussion points that address or highlight: a. Key points for care based on what is known now—as limited as that may be (perhaps in the Discussion or even more suited for the Evidence Gaps subsection on page 26)	We appreciate this suggestion but have intentionally avoided statements on clinical implications. The primary goal was to describe the volume of studies and whether sex effects have been examined. Without a careful quality assessment, we are hesitant to suggest clinical actions

Question Text	Reviewer Number	Comment	Response
		as a result of the health evidence map. Suggesting content along the lines of clinical implications. b. Future directions/research gaps. This could be a separate section or become part of a slightly re-worked section that is currently titled: Prioritizing Areas for Evaluation of Sex Effects. The content of that "prioritizing areas" is broad and speaks to the pressing need for researchers to incorporate adequate methodology to address sex effect questions within their projects. The content I would recommend adding (here or elsewhere) are gaps within the content areas of depression, DM, and chronic pain that would provide recommendations for the scientific community on possible future directions.	based on the estimates of intervention effects that we report. Thank you for this suggestion. We've added example of gaps and types of studies that could be conducted to address these gaps for the conditions reviewed. We've also discussed the potential clinical implications of results from these proposed studies.
	4	In general, I found this evidence map to be difficult to follow and to review. I believe this is attributable primarily to the enormous scope of the review. Attempting to provide brief overviews of the evidence for all of the interventions in all three huge clinical areas has resulted in extremely superficial and potentially misleading summaries of evidence for the individual interventions and conditions. The overview approach also obscures and detracts from the findings on sex effects, which is the main focus and strength of the report. (For example, the evidence for medications in chronic LBP, see specific comment below.) I think these problems could be substantially addressed by focusing just on evidence (and lack thereof) regarding sex differences. Specific comments: 1. The definition and merits of individual patient data (IPD) meta-analysis should be briefly described (and citations provided) in the methods section. Also, as IPD is an unfamiliar abbreviation, it should be included in the abbreviation list and spelled out in the table footnotes.	Thank you for this comment. We agree that the scope is large and the key messages could be difficult to identify with the current report structure. Therefore, we've substantially reorganized the report to consolidate the findings on sex effects across the three conditions. We've moved the information on intervention effects in general to an Appendices (by condition), as these were not the primary focus of our evidence map. We've added a definition for IPD meta-analysis to Table 2 (Definitions of statistical approaches) and added a brief rationale for the merits of this approach to the methods section. We've been careful to define this abbreviation when used in tables.

Question Text	Reviewer Number	Comment	Response
		2. The choice to limit reviews to the past 5 years may create an unintended bias for lower quality reviews in fields with few large funded RCTs (such as chronic low back pain). If a definitive high quality review has been published and no new trials are available, subsequent reviews are unlikely to be higher quality.	Limiting reviews to the past 5 years was based on the rationale that reviews older than this are often out of date. Although we agree this decision could lead to missing reviews on some interventions (*eg*, no recent published review), we disagree that it would introduce a bias toward selecting low-quality reviews.
		3. Brief presentation of review findings without any details or quality assessment is potentially misleading. In the pain section in particular, included reviews have limitations that are not acknowledged and some of the best quality reviews seem to be absent.	We agree that brief presentations of intervention effects without quality assessment could be misleading. We've addressed this in several ways. First, we reorganized the report to emphasize sex effects, where we offer more information on review author's comments on the quality of the evidence, and provide discussion of the limits of certain analytic techniques (*ie*, meta-regression vs IPD meta-analyses). We have also added statements in the Methods and Results sections cautioning readers that the reviews have not been assessed for quality and thus estimates of effect may be wrong.
		4. Page 22, line 41-42: The two reviews were not of "joint injections." One reviewed facet joint injections and the other reviewed epidural injections. Also, I believe the authors meant to say "reduction in pain" or "improvement in pain relief", rather than "reduction in pain relief." Without information about the quality of the reviews, the comparisons, the specific pain indication, or the time frame of the outcomes, the summary statement about improvement may be misleading. (In general, very short term improvement in pain is not considered clinically important in the setting of chronic pain.)	We had defined the term "joint injections" loosely and have now specified these injections as facet and epidural. We have made the edit to "reduction in pain." We agree that without information about quality, etc., summary statements may be misleading. Therefore, throughout the report, information on general (*ie*, non-sex-specific) effects of interventions has been moved to Appendices, partially due to several reviewers' correct observation that it had not been collected as rigorously.
		5. Page 22, lines 54-59: The description of this meta-analysis is confusing. It was an indirect (no direct comparisons) meta-analysis of 15 placebo-controlled trials that was sponsored by Eli Lilly with the purpose of comparing duloxetine to other analgesics. It included trials of several typical opioids ("narcotics" "scheduled opioids"), tramadol ("non-scheduled opioids"), duloxetine, paroxetine	This information has been moved to an appendix and therefore gets less emphasis. We added the modifier that this was an industry-sponsored study. We did not add an extensive discussion of the strengths and weaknesses of the review, since we did not quality-rate the studies or include this type of discussion for other reviews.

Question Text	Reviewer Number	Comment	Response
		("SSRIs"), and etoricoxib ("NSAIDS"). For a variety of reasons (controversial methods, differences in trial designs between drugs), their findings require additional discussion and context. Also, this should not be the only systematic review of medications for LBP.	
	5	page 7: I had some trouble following the literature flow chart (Figure 1). I wonder if it would be better to break down the figure into 3 smaller figures for depression, diabetes and chronic pain. Page 10: did any of the depression studies report on menopausal status? page 25: the second paragraph notes the percentage of studies evaluating sex as a moderator (19%; 9%; 5%). I think this information should be added to the abstract.	We considered this suggestion but decided a single figure was preferable. However, we revised the figure for clarity. This is an interesting question but we did not abstract data on menopausal status. We have added this information to the Abstract.
	7	Thank you for this very thorough review. I can only say that I am disappointed in the findings (that very few studies addressed gender differences) not in the quality of the report which was very complete. They only thing I might have considered is including a longer time frame since the last 5 years seemed very short, especially for pain and depression related findings.	We agree it is disappointing that so few studies address sex effects. Limiting the review to the past 5 years was based on the rationale that reviews older than this are often out of date. At this time, we are not able to extend the timeframe for included systematic reviews.
	8	This report is very clearly written and laid out and tackles an important issue within and outside the VA, which is the extent to which sex/gender differences are examined systematically as well as the potential for the larger non-VA literature to help identify opportunities for leveraging national investments in research for use in improving women Veterans' care in the VA health care setting. The review also focuses on top priority conditions of high prevalence and quality of life impact for men and women, offering opportunities to consider differences and potential disparities in a broad way even though this is focused and	Thank you for these comments.

Question Text	Reviewer Number	Comment	Response
		framed as a Women's Health Evidence Map. Given women's numerical minority in VA, this framing is appropriate. The writing and methods are clear and easy to read and follow. The material provided is solid and usefully displayed. Modest issues arise in use of abbreviations throughout the tables and figures, which warrant attention. For example, Figures 4 and 5 on pages 14 and 15 have "psyched" as an abbreviation and while this is likely for psychoeducation, the "psyched" abbreviation has other meanings in our vernacular so some other abbreviation without alternative interpretation would be helpful. The Discussion (and thus Abstract in part) would benefit from clearer presentation of the main takeaway messages. Emphasis appears, perhaps unintentionally, to be on studies often showing greater benefit in women. However, the first takeaway point would seem to take precedence, *ie*, that a remarkably small fraction of the investment in these trials has been on examining sex/gender differences. The policy implications, however, of readers focusing on the positive findings in that small fraction that examined these issues are potentially very significant and may suffer from publication bias and other issues. In other words, the efforts to require inclusion of women in trial enrollment, analysis and reporting has been underway for decades, with substantial evidence that women's response to pharmaceutical agents, for example, can be meaningfully clinically different than men's. So your primary takeaway message appears to be that this emphasis has failed despite regulatory requirements. Very little time is spent on this failure in the Discussion so the findings lack contextualization. Instead, much more time is spent on the summary of sex effects in the very small fraction of studies that bothered to report on sex/gender differences, and given publication biases toward positive results, we lack adequate knowledge of what might have been found in the	 We were able to spell out terms within the figures, and included abbreviation callouts where needed. We've revised the discussion to address the issues you raise. These changes include moving the summary of sex effects to the results section, moving the table of gaps in evidence to an earlier section of the discussion, and giving more emphasis in the text to the general paucity of studies evaluating sex-specific effects.

Question Text	Reviewer Number	Comment	Response
		large majority that failed to examine these issues. The findings that were gleaned from the review are nonetheless of value, but they are not the whole story -- the concern is that they will become the whole story for those looking to avoid the methodological investment of time and resources needed to more definitively characterize intervention effects by subgroup. Page 27: Very little information is included with respect to what VA has done to increase inclusion of women Veterans in VA research through the Women's Health Research Network, which includes consortium development (*ie*, training of VA investigators on issues around women Veterans' health and health care; training in oversampling techniques and subgroup analysis approaches) and development of a national practice based research network that facilitates inclusion of women by developing local VA facility capacity to identify, recruit and retain women in VA research. This network is probably worth mentioning/citing, as it is also now responsible for increasing inclusion on women in the VA Cooperative Studies Program. Suggest you consider the following references to support building up this particular and brief paragraph: Frayne SM, Carney DV, Bastian L, Bean-Mayberry B, Sadler AN, Klap R, Phibbs CS, Kimerling R, Vogt D, Yee E, Lin J, Yano EM. The VA women's health practice-based research network: Amplifying women veterans' voices in VA research. J Gen Intern Med. 2013;28(Suppl 2):S504-S509. Bielawski MP, Goldstein K, Mattocks KM, Bean-Mayberry B, Yano EM, Bastian LA. Improving care of chronic conditions for women veterans: What we have learned from comparative effectiveness research. J Comparative Effectiveness, 2014 Mar;3(2):155-166.	Thank you for your comment and suggestions. We have expanded our discussion of VA initiatives to encourage research on women's health topics and improve inclusion of women Veterans in VA research.

Question Text	Reviewer Number	Comment	Response
		Yano EM. A partnered research initiative to accelerate implementation of comprehensive care for women Veterans: The VA Women's Health CREATE. Med Care. 2015 Apr;53(4 Suppl 1):S10-14. I think this report is going to have substantial impacts within and outside the VA both for advancing the tenets of equitable benefits of our research investment by gender and for informing ongoing opportunities for reducing gender disparities and also for targeting scarce resources more efficiently when differences do not indeed exist.	

APPENDIX E. OVERALL EFFECTS OF SELECTED INTERVENTIONS: DEPRESSION

The information provided in this appendix reflects what was reported by the authors of the original, primary publication. We have not separately assessed the article for quality or accuracy.

Effects by Diagnostic Group for Depressive Disorders

Major depressive disorder or depressive disorder. *Antidepressants* were evaluated using IPD meta-analysis,[42-50] multiple treatment comparison meta-analysis,[34,203] conventional meta-analysis,[56,58,204-207] qualitatively,[57] and using mixed approaches.[208] A review of 165 antidepressant trials in patients with major depressive disorder found clinical response rates of 54.3% for antidepressants and 37.9% for placebo.[204] The most comprehensive comparative effectiveness review (n=234 studies) used a multiple treatment comparison analysis to compare different antidepressants.[34] This study, conducted by an EPC, found that antidepressants were effective and that there were no clinically important differences in efficacy or effectiveness between antidepressants for acute- or continuation-phase treatment. Subgroup analyses did not show differences in treatment effects by age, sex, ethnicity, or comorbid condition.

Five reviews evaluated antidepressants for late-life depression.[34,44,45,56,208] Results were inconsistent with some reviews finding antidepressants less effective for older adults (>65 years of age) than for younger adults.[44,208] Other reviews found no moderating effect of older age.[34] Antidepressants were associated with decreased suicidal risk in older (≥65 years of age) and younger adults.[45]

Psychotherapy for depressive disorders was examined in 35 reviews.[32,33,35-38,52-54,60,209-233] Reviews evaluating multiple therapies (n=92-132 included trials) found psychotherapy compared with inactive control more effective for reducing depressive symptoms (n=117; SMD 0.67, CI 0.60 to 0.75), and psychotherapy increased the proportion of patients with a clinical response or clinical remission.[60,211] Therapies examined included cognitive behavioral therapy (CBT), problem-solving therapy (PST), short-term psychodynamic therapy, interpersonal therapy, behavioral activation, and nondirective counseling. However, when accounting for publication bias (SMD 0.42) or when restricting analyses to the highest quality studies (Cohen's d 0.22), effects were diminished.[33,210] Effects did not differ significantly for different types of psychotherapy. Therapy was more effective than control for improving hopelessness but not suicidality.[210] For major depressive disorder and subsyndromal depression, psychotherapy did not differ from antidepressant medication but was less effective than antidepressants in patients with dysthymia.[37,215,228] Four reviews evaluated psychotherapy in older adults, finding the strongest evidence of efficacy for CBT (n=14; Hedges' g -0.57, CI -0.80 to -0.34).[216,223,224,227]

Reviews concluded that CBT is effective in individual and group formats.[224,226] Four reviews evaluated computerized therapy (predominately based on CBT) compared with inactive control or treatment as usual for patients with depressive disorders.[230-233] Consistent with the other reviews, the largest identified 19 RCTs and found computerized therapy effective for depressive disorders (n=19; Cohen's d -0.56, CI -0.71 to -0.41).[232] An ESP review found that 6 to 8 sessions of CBT or PST improved depressive symptoms more than control (n=7; SMD -0.42, CI -0.74 to -0.10) for patients recruited from primary care settings.[36] Cochrane reviews concluded that

low-quality evidence suggested that third-wave therapy (*eg*, behavioral activation, acceptance and commitment therapy) may be effective and similar to other psychotherapies.[32,35]

Seven reviews evaluated a *combination of antidepressants plus psychotherapy* compared with one of these treatments alone for acute-phase treatment of depressive disorders.[55,234-239] The largest review found greater reduction in depressive symptoms for combined treatment than for antidepressants alone (n=23; Hedges' g 0.43, CI 0.29 to 0.57).[237] Another review found a small benefit from combined treatment compared with psychotherapy plus placebo pill (n=16; Cohen's d 0.25, CI 0.03 to 0.46).[235]

Seven reviews evaluated *aerobic exercise* compared with other physical activity, antidepressants, or treatment as usual.[240-246] Exercise was more effective than control with effect sizes ranging from small to moderate. [243-246] Aerobic exercise was not more effective than other physical activity (n=8; SMD 0.01, CI -0.23 to 0.24) or antidepressants. [240] However, aerobic exercise improved depressive symptoms when used to augment treatment as usual (n=4; SMD -0.44, CI -0.79 to -0.09).[240,241] A single review of yoga[242] found evidence that yoga was more effective than usual care. These reviews did not examine sex effects.

A single IPD meta-analysis evaluated low-intensity *self-help interventions* for depressive disorders or mixed depression and anxiety.[41] Self-help interventions were more effective than treatment as usual for reducing depressive symptoms (n=16 comparisons; SMD -0.42, CI -0.55 to -0.29). An analysis of potential moderators of intervention effects suggested that intervention effects did not vary by sex but were greater as baseline severity increased.

Three reviews evaluated *quality improvement interventions* that were predominately a form of collaborative care.[40,59,247] The largest review[247] identified 40 trials, finding moderate benefit on depressive symptoms for collaborative care compared with treatment as usual or other enhanced care (Cohen's d 0.31, CI 0.16 to 0.47).

Dysthymia/persistent depressive disorder. Six reviews evaluated interventions for dysthymia.[51,55,204,248-250] A multiple treatment comparison meta-analysis found antidepressants more effective than placebo (n=45; OR for response 2.35 to 6.98 for various antidepressants).[249] A conventional meta-analysis also found antidepressants more effective than placebo (n=9; RR for response 1.75, CI 1.49 to 2.04).[204] There were no differences in treatment response between SSRIs and tricyclic antidepressants, but dropouts were fewer with SSRIs (n=7, RR=0.41; CI 0.19, 0.86).[250] Psychotherapy was more effective than control for reducing depressive symptoms (n=8; Cohen's d 0.23, CI 0.06 to 0.41) but less effective than antidepressants (n=10, Cohen's d -0.31, CI -0.53 to -0.09).[55,248] In one review, interpersonal psychotherapy plus antidepressants was more effective than antidepressants alone (OR 1.83),[249] but in another review, combined treatment was not more effective than antidepressants alone for patients with chronic major depressive disorder, dysthymia, double depression, or recurrent depression (n=8; RR for response 1.20, CI 0.98 to 1.48).[51] No other interventions were evaluated.

Subyndromal/minor depressive disorder. Two reviews evaluated psychotherapy in older adults with subsyndromal depression.[251,252] In the larger review,[252] psychotherapy, including CBT, PST, and behavioral activation, was more effective than wait-list, placebo pill, or treatment as usual controls (n=5; 701 patients; no effect estimate). A single review[253] identified 8 trials evaluating antidepressants for subsyndromal depression or mild major depressive disorder. Antidepressants showed small improvements for depressive symptoms compared with placebo

(n=2; MD Hamilton Depression Rating Scale -1.39, CI -2.41 to -0.36). None of these reviews evaluated sex effects, and no other interventions were evaluated.

Treatment-resistant depression. Three reviews evaluated interventions for treatment-resistant depression and found the evidence sparse.[39,254,255] Mindfulness-based cognitive therapy plus treatment as usual was more effective than treatment as usual in 2 trials (MD on Beck Depression Inventory -10.28, CI -17.18 to -3.38).[254] Compared with active management, an ESP review identified 2 good-quality trials that showed similar benefit from augmenting antidepressant treatment with other antidepressants or psychotherapy, or switching antidepressants.[39] None of these reviews evaluated sex effects, and no other interventions were evaluated.

Relapse prevention. Seven reviews evaluated interventions for treatment-resistant depression.[34,214,254,256-259] Psychotherapy alone or in combination with an antidepressant decreased the risk of relapse (n=8; RR=0.79, CI 0.66 to 0.96).[258] Specific therapies that were found effective were group or individual CBT,[256,258] interpersonal therapy,[214] and mindfulness-based cognitive therapy.[254,258,259] Antidepressants (primarily SSRIs and SNRIs) were effective in preventing relapse (n=54; OR for relapse 0.35, CI 0.32 to 0.39) in patients who had responded to an antidepressant.[257] An EPC-conducted multiple treatment comparison meta-analysis found no clinically important differences in efficacy between different antidepressant medications.[34] None of these reviews evaluated sex effects, and no other interventions were evaluated.

APPENDIX F. OVERALL EFFECTS OF SELECTED INTERVENTIONS: TYPE 2 DIABETES

The information provided in this appendix reflects what was reported by the authors of the original, primary publication. We have not separately assessed the article for quality or accuracy.

Effects by Interventions for Diabetes

Medications. Of 120 eligible reviews on medications, we performed full data extraction on 75, prioritizing those that evaluated multiple drug classes or addressed less frequently examined categories (*eg*, meglitinides), among other criteria (see Methods). Glycemic control (n=38; reviews) and weight (n=25) were the most frequently included outcomes. Cardiovascular events (n=12) and mortality (n=16) were evaluated less often. Among adverse events, hypoglycemia was the most frequently discussed (n=29). The largest review, originating from an organization known for high-quality reviews, focused on risk for lactic acidosis associated with metformin therapy and included 347 studies.[78] This study evaluated 70,490 patient-years of metformin use compared with 55,451 patient-years among nonusers, with 39% of women among both users and nonusers, and found no reported cases of lactic acidosis. The upper bound for the true incidence was estimated to be 4.3 cases per 100,000 patient-years among metformin users compared with 5.4 cases for nonusers.[78]

The next largest review included 277 RCTs, with 46% women overall, and examined effectiveness (dichotomously defined as reaching hemoglobin A1c target or not) and risk for adverse events for multiple drug classes compared with metformin.[260] This review used network meta-analysis, conducting 173 direct and 180 indirect comparisons. Most drug classes were found to improve the likelihood of achieving glycemic targets when added to existing metformin therapy, ranging from the lowest benefit for rosiglitazone (OR 1.2, CI 1.1 to 1.3) to the highest for glucagon-like peptide 1 agonists (OR 11.1, CI 3.4 to 35.9). Sulfonylureas (OR 3.95, CI 1.82 to 8.55), a-glycosidase inhibitors (OR 3.24, CI 1.69 to 6.24), and meglitinides (OR 3.25, CI 1.83 to 5.75) were all associated with increased risk for hypoglycemia when added to metformin.[260]

Bariatric surgery. Of 12 reviews on bariatric surgery, only 3 were restricted to RCTs.[261-263] Weight loss and diabetes remission were evaluated by nearly all reviews. The 3 largest and most recent reviews included 39 studies,[100] 35 studies,[264] and 33 studies.[265] One of these reviews examined multiple surgical procedures and reported sex effects on diabetes remission (key results reported above).[100] The other reviews evaluated gastric banding versus multiple comparators,[264] and gastric bypass versus sleeve gastrectomy.[265] Gastric banding was associated with average 47% excess weight loss over 2 years.[264] There were no differences in rates of diabetes remission (67% and 81% at 3 and 36 months for gastric bypass, compared with 56% and 80% for sleeve gastrectomy) or in excess weight loss between the 2 procedures.[265]

Psychoeducation and mixed behavioral interventions. Six reviews investigated the effect of psychoeducation and/or mixed behavioral interventions on glycemic control (n=6 reviews) and/or weight (n=3 reviews). Included studies ranged from 13 to 33, and 4 reviews were restricted to RCTs.[79,83,106,266] Three reviews reported proportion of women included in primary studies (range 45% to 70%),[102,266,267] and one specifically evaluated treatment effects in minority women.[102]

Four reviews evaluated mixed interventions consisting of psychoeducation and exercise with or without dietary advice.[79,83,102,106] The other 2 mixed interventions included mobile phone applications[267] and internet-based self-management strategies.[266] The largest review (n=33 studies) was conducted by the Cochrane collaboration, and examined culturally appropriate health education and exercise in ethnic minority groups in middle- and upper-income countries.[83] There was high-quality evidence to support that these interventions reduced HbA1c at 6 months (n=14; MD -0.53%, CI -0.72% to -0.35%), with some sustained effect at 12 months (-0.2%) and 24 months (-0.3%). There were no statistically significant effects on body mass index. Subgroup analyses were not performed. Another review, based on a 2011 AHRQ report, inspected the progression of diabetes-related complications and found significantly decreased risks of peripheral neuropathy, nonfatal myocardial infarction, and death with lifestyle interventions at 13.3 years of follow-up.[79] There were no significant differences in risk for retinopathy or nephropathy between the intervention and control groups.

One review of internet-based self-management provided qualitative results showing that psychoeducation and behavioral techniques via mobile phone applications were associated with improved HbA1c (n=10; WMD -0.81, CI -1.11% to -0.50%).[267]

Supervised exercise. Of 14 reviews on supervised exercise, 10 were restricted to RCTs, and the number of included studies ranged from 2 to 34. Six systematic reviews reported proportions of women in primary studies (median 53%, range 3% to 88% female), but none reported sex effects. Nearly all reviews (n=13) reported results for glycemic control, while 4 reported on weight loss,[74,268-270] and 6 reported other outcomes.[74,269,271-274] None reported adverse events.

Five reviews compared the effects of aerobic exercise, resistance exercise, and combinations of the 2 on HbA1c.[268,269,275-277] The largest and most recent review restricted to RCTs included 26 primary studies with a minimum intervention duration of 12 weeks.[276] This review found that all forms of exercise reduced HbA1c (aerobic MD -0.70%, CI -1.02% to -0.38%; resistance MD -0.62%, CI -1.14% to -0.11%; combined MD -0.47%, CI -0.64% to -0.31%) and that exercise volume (*ie*, frequency and duration) is a main determinant of the effect on glycemic control. However, a slightly older review that included 34 RCTs with a minimum treatment duration of 8 weeks reported that combined aerobic and resistance exercise improved glycemic control more than aerobic exercise alone (MD -0.67%, CI -0.93% to -0.40%; MD -0.60%, CI -0.98% to -0.27%, respectively).[268]

Five reviews investigated only resistance exercise[271,274,278] or aerobic exercise alone.[270,273] All reported improved HbA1c for intervention groups compared with control. Four reviews examined other specific types of exercise. Of these, 3 reviews examined tai chi,[272,279,280] and one investigated yoga[74]; none found a statistically significant effect on glycemic index, weight, or cardiovascular risk.

Dietary interventions. Four eligible reviews on dietary interventions were restricted to RCTs and reported on both HbA1c and weight/BMI.[105,281-283] Adverse events were not reported, and none reported gender distribution or sex effects. None originated from an organization known for high-quality systematic reviews. The number of trials ranged from 8 to 20.

The largest review (n=20 studies)[105] examined 6-month outcomes after various dietary interventions (*ie*, high fiber, high protein, low carbohydrate, low glycemic index, Mediterranean,

vegan, or vegetarian) compared with one of multiple control diets (*ie*, ADA, high glycemic index, low fat, or low protein). This review concluded that the Mediterranean diet was the most effective at decreasing HbA1c (n=3; MD -0.41%, CI -0.58% to -0.24%) while low-carbohydrate (n=7; MD -0.12%), low glycemic index (n=3; MD -0.14%), and high protein (n=2; MD -0.28%) were all more effective than diets with higher carbohydrate content. Both the Mediterranean and low carbohydrate diets produced weight loss (MD -1.84 and -0.69 kg, respectively), but the difference was statistically significant only for the Mediterranean diet.

Quality improvement. Three reviews evaluated different quality improvement strategies. None provided the gender distribution of included studies and none reported sex effects. The largest review (n=52 studies) examined the effect of care management on glycemic control.[75] Statistically significant reductions in HbA1c were found (WMD -0.22%, CI -0.40% to -0.04%), but given high heterogeneity, the authors suggested these results were unlikely to be important. The second eligible review included 26 studies, which investigated 9 quality improvement strategies applied to rural settings.[284] Quality improvement was more effective than control for reducing HbA1c (MD -0.41%, CI -0.75% to -0.07%), and subgroup analyses showed that using multiple strategies and a community setting for interventions were more effective compared with fewer strategies or a clinical setting, respectively. The third review (n=20 studies) was restricted to RCTs that evaluated computerized decision support systems (CDSS) in primary care.[73] This qualitative synthesis reported that CDSS alone or with reminders improved process of care but did not affect health outcomes, whereas when CDSS was combined with feedback on self-management performance or case management, HbA1c improved.

APPENDIX G. OVERALL EFFECTS OF SELECTED INTERVENTIONS: CHRONIC PAIN

The information provided in this appendix reflects what was reported by the authors of the original, primary publication. We have not separately assessed the article for quality or accuracy.

Effects by Chronic Pain Condition

Chronic low back pain. Twelve reviews evaluated *exercise* for CLBP.[127,128,130,131,133,285-291] One additional review compared acupuncture, spinal manipulation, and exercise.[292] Exercise interventions included yoga and Pilates (n=6 studies),[127,128,131,133,290,291] core stability, aerobic or general exercise,[130,286] mixed programs,[285,287-289] and nonspecific programs.[292] The largest review (n=40) found that all types of exercise compared with minimal care improved pain (MD -4.83 [100-point scale], CI -9.36 to -0.30) and disability (MD -6.41, CI -9.76 to -3.05). The number of exercise sessions was significantly associated with increasing effect sizes on pain, suggesting that for each additional session, the effect size would increase by 0.13 (CI 0.02 to 0.24).[288] Another review of similar size (n=39 studies) found that strength/resistance (n=11; ES: -0.50, CI -0.77 to -0.24) as well as coordination/stabilization-focused exercise programs are effective in reducing pain (n=12, ES -0.47, CI -0.77 to -0.18).[285] Four reviews found moderate evidence of yoga or Pilates reducing pain over short-term, but not long-term, follow-up (largest review n=4; SMD -0.61, CI -0.97 to 0.26),[127,128,131,133] while 2 reviews found no significant effect on pain or functionality (n=4) when comparing Pilates with no treatment or lumbar stabilization.[290,291] Adverse events were rarely reported for exercise interventions.

Five reviews[129,293-296] and one IPD meta-analysis[168] evaluated either *acupuncture* or *chiropractic manipulation* compared with usual care, no treatment, or sham intervention. One additional review compared acupuncture, spinal manipulation, and exercise.[292] The largest review of acupuncture (n=32 studies) reported significant reductions in self-reported pain (n=3-4; SMD -16.76 to -0.72; CI -33.33 to -0.19) and overall function (n=3-4; SMD -0.94 to -0.36; CI -1.61 to -0.04).[129] However, significant, unexplained variation in treatment effects limit these findings. Another review found acupuncture to be more effective in reducing pain compared with sham acupuncture (n=5; SMD 0.20; CI 0.09 to 0.32) or no intervention (n=5; SMD 0.49; CI 0.33 to 0.64).[168] The most recent large review of chiropractic manipulation (n=26 studies) reported significant but not clinically relevant effects on short-term pain relief (SMD -4.16; CI -6.97 to -1.36) and functional status (SMD -0.22; CI -0.36 to -0.07).[294] Manual therapy was no more effective than sham intervention or exercise.[293]

Two reviews evaluated *injections* (one on facet joint and the other on epidural), and using qualitative synthesis, found fair evidence for reduction in pain.[297,298] Complications were rare. One additional large qualitative review examined multiple nonsurgical interventional therapies for low back pain, finding that epidural steroid injections were moderately effective for short-term but not long-term symptom relief. There was insufficient evidence for other interventional therapies for chronic low back pain, including facet joint injection and intradiscal steroid injection.[299] Sex effects were not examined in any review.

One Cochrane review evaluated 30 trials of *behavioral therapy* compared with waitlist or usual care controls for CLBP.[173] Operant behavior therapy was more effective than waitlist control (n=3; SMD -0.43, CI -0.75 to -0.11), and behavioral treatment was more effective than usual care

for short-term pain relief (n=2; MD -5.18, CI -9.79 to -0.57). This review did not examine sex effects. Another review[300] that evaluated many types of interventions (n=70) examined 21 behavioral studies and agreed with the conclusions of the Cochrane review. One review tested neurophysiological education only, but did not find clinically significant changes.[301]

One industry-sponsored review of *medications*, using indirect meta-analysis, evaluated serotonin norepinephrine reuptake inhibitors (SNRIs) and SSRIs compared with NSAIDs, tramadol, and narcotics and found that, compared with placebo, scheduled opioids were most effective in reducing pain (n=8; SMD -0.39, CI -0.47 to -0.31), followed by nonscheduled opioids, Cox II inhibitors, and duloxetine.[126]

One review of QI interventions evaluated pain rehabilitation programs compared with controls.[132] This review identified 18 trials, finding a moderate effect of pain rehabilitation programs on improving disability (beta=0.429, SE=0.160, p=0.0009) and quality of life (beta=0.417, SE=0.033, p<.001).

Fibromyalgia. Of the 34 reviews of FM interventions, 11 were conducted by an organization known for high-quality reviews.[134-137,141,144,147,150,153,161,302] Fourteen examined *medication treatment* for FM: 7 for antidepressants[134-140] 5 for anticonvulsant agents,[137,141-144] and 2 for both classes of drugs.[145,146] Of the reviews of different antidepressant drug classes, one examined a tricyclic agent,[135] and 3 focused on SNRIs.[134,136,137] A review that included 7 studies focusing specifically on FM found that amitriptyline reduced pain more than placebo with an RR of 2.9 (CI 1.7 to 4.9) based on 4 studies with second-tier data.[135] Another review that included 10 studies focused on FM found that SNRIs, specifically duloxetine and milnacipran, had small beneficial effects on both pain with a SMD -0.23 (95% CI -0.29 to -0.18), and quality of life with a SMD of -0.20 (95% CI of -0.25 to -0.14).[134] For this review of SNRIs, the intended subgroup sex effects analyses for outcome of pain were not conducted due to lack of available individual patient-level data. This same review noted no difference between placebo and SNRI with respect to serious adverse effects, though more patients withdrew for adverse events in the SNRIs arms than in the placebo arm with an RR of 1.83 (CI 1.53 to 2.18). Additional reviews that focused solely on milnacipran,[137] duloxetine,[136] or a mixture of SNRIs, milnacipran, SSRIs, and tricyclic antidepressants supported the above findings related to pain relief.

The anticonvulsant agents gabapentin and pregabalin were found to improve pain in 5 reviews.[141-144,302] In one trial of 150 patients included in the most recent of these reviews,[302] gabapentin was noted to decrease pain more than 30% from baseline at 2400mg daily versus placebo with an RR of 1.6 (CI 1.07 to 2.42). Similarly, pregabalin reduced fibromyalgia pain 50% compared with placebo (RR 1.59, CI 1.33 to 1.90) based on high-quality evidence from 5 studies including 3256 patients,[141] and an RR of 1.5 to 1.7 in a second review at doses 300mg to 600mg per day.[142] A dose-response relationship with pregabalin was also noted for both pain control and adverse events,[142,143] which were most frequently dizziness and somnolence.[142,302] Serious adverse events were not higher with anticonvulsant treatment.

We identified 6 reviews with meta-analyses that included trials of various forms of *exercise* as treatment for pain associated with FM.[147-152] Four of 5 types of exercise were found to decrease pain when compared with placebo, but it is less clear if any types of exercise are superior compared with other forms of exercise. Specifically, low- to moderate-quality evidence from 7 studies suggests that supervised aquatic exercise training causes moderate decreases in pain with

an MD of -6.59 (CI -10.71 to -2.48) on a 100-point scale; but this review did not find a significant improvement in pain compared with land-based exercise.[147] Another review[152] also found improvement with aquatic therapy, especially if the duration was at least 20 weeks. Aerobic exercise was also found to lead to significant reductions in pain with an SMD of -0.31 (CI -0.46 to -0.17).[148] In a multiple treatment comparison analysis, low-quality evidence suggests that moderate to high-intensity resistance exercise training reduces pain in FM.[150] Adverse effects related to aerobic exercise were infrequent.[148]

Results for *meditative movement therapies* (MMT) such as yoga, tai chi, and qigong were conflicting. One review evaluating 7 studies found that these therapies did not reduce pain but may improve health-related quality of life.[149] Another review found a medium-to-high effect size for MMT based on weak data.[151] In both reviews, MMT was found to be safe with a low rate of dropout due to adverse events in one review[149] and no serious adverse events in the second.[151]

Six reviews examined different types of *behavioral interventions*.[153-158] One review of 21 studies conducted in adults with FM found low-quality evidence that CBT compared with control produced an end-of-treatment benefit of 0.5 points on a scale from 0 to 10 with respect to pain (SMD -0.27, CI -0.47 to -0.07) and a benefit of 0.7 points for reducing disability (SMD -0.30, CI -0.51 to -0.08).[153] Another review of 23 studies found that CBT produced a moderate positive effect on pain (n=8; Hedge's g 0.60, CI +0.43 to +0.76). Psychological treatments other than CBT had a smaller effect size (n=18; Hedge's g 0.27, CI +0.17 to +0.37)[158] Mindfulness-based stress reduction also led to a small beneficial effect on FM-related pain[155,156] and quality of life,[155] based on generally low-quality evidence. The same was true of electromyogram-based biofeedback, but not electroencephalogram-based biofeedback.[157] No specific information was noted about adverse events.

Five reviews examined *acupoint stimulation/acupuncture* for FM[159-163] and came to similar conclusions. These reviews included from 9 to 16 RCTs. Compared with sham acupuncture, acupuncture did not significantly reduce FM-related pain. Based on one RCT with 16 participants, acupuncture did appear to be more effective than no treatment with an RR of -30.19% (CI -55.23% to -5.15%) and more effective as an adjunct to standard therapy based on one RCT with 58 patients with an RR of -37.50% (CI -48.75% to -26.25%).[161] There was some low-quality evidence that acupuncture is more effective at reducing pain than medications.[159-161] Electro-acupuncture may be better than manual acupuncture at pain reduction.[161] That review concluded there is insufficient information about adverse events to draw definitive conclusions; however, another review[162] reported adverse effects from 8 of 25 studies as bruising, nausea, fainting, discomfort with needles, and temporary edema of the hand. One trial reported that a patient had mild scalding on the skin after being included in a cupping group. One review examined 4 studies of chiropractic care for FM and concluded that there was no significant difference between intervention and control groups.[164]

Knee OA. We identified 8 reviews that examined intervention effects on pain due to knee OA.[165-172] One large review evaluating 54 trials found high-quality evidence that land-based *therapeutic exercise* significantly reduced pain compared with control (nonexercise or nontreatment) with an SMD -0.49 (CI -0.39 to -0.59).[167] Eight studies included measurement of serious adverse events, and none were reported. Similar, a review of pre-operative interventions included 4 trials which found that exercise programs significantly decreased pain from knee OA

with a SMD -0.43 (CI -0.13 to 0.73).[170] One review of 7 trials of proprioceptive-based exercise found no improvement in pain and a small improvement in function.[303]

One review of *medications* used a multiple treatment comparison meta-analysis to examine the effects of topical NSAIDs for pain in patients with chronic musculoskeletal pain.[166] The review included 34 studies, 16 of which focused on knee OA. Topical NSAIDs were more effective than placebo (RR 1.29 for 50% pain reduction or equivalent measure; CI 1.21 to 1.38) but not more effective than oral NSAIDs for pain in the context of osteoarthritis (RR 1.02, CI 0.94 to 1.11). Topical NSAIDs led to fewer gastrointestinal side effects than oral NSAIDs but led to an increase in local adverse events (mostly skin-related). This review did not evaluate sex effects.

Three reviews examined injections for knee OA. One review[165] examined the trajectory of intra-articular hyaluronic acid therapeutic effects on knee OA and found a beneficial effect on pain that peaked at 8 weeks post-injection (n=54; ES 0.46, CI 0.28 to 0.65), diminishing to a small effect at 24 weeks (ES 0.21, CI 0.10 to 0.31).One review [172] considered 4 RCTs and 2 studies that compared platelet-rich plasma (PRP) injections as compared with intra-articular normal saline or hyaluronic acid. Based on 4 studies, this review found that PRP led to greater improvements in the WOMAC, a composite score[304] of pain, stiffness and function with an MD of -18.0 (-28.8 to -8.3). Of note, they report that there was an increase in nonspecific adverse events among those who received PRP versus control (8.4% vs 3.8%). A third review of 6 RCTs found no benefit of joint lavage on pain due to knee OA.[169] None of these reviews evaluated sex effects.

One review using IPD meta-analysis of 31 studies examined *acupuncture* for chronic pain including 9 studies of knee OA.[168] Acupuncture decreased pain of knee OA compared with both no acupuncture (SMD 0.57, CI 0.29 to 0.85) and sham acupuncture (SMD 0.37, CI 0.03 to 0.72). This review did not evaluate sex effects.

APPENDIX H. SYSTEMATIC REVIEW REFERENCES BY CONDITION

This appendix lists full citations for included systematic reviews in alphabetical order by condition. The asterisk beside a reference indicates the review reported sex effects.

Depressive Disorders (86)

Andrews G, Cuijpers P, Craske MG, et al. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PLoS One 2010;5(10):e13196. PMID: 20967242.

Baardseth TP, Goldberg SB, Pace BT, et al. Cognitive-behavioral therapy versus other therapies: redux. Clin Psychol Rev 2013;33(3):395-405. PMID: 23416876.

*Bower P, Kontopantelis E, Sutton A, et al. Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data. BMJ 2013;346:f540. PMID: 23444423.

*Braun SR, Gregor B, Tran US. Comparing bona fide psychotherapies of depression in adults with two meta-analytical approaches. PLoS One 2013;8(6):e68135. PMID: 23840824.

Bridle C, Spanjers K, Patel S, Atherton NM, Lamb SE. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. 2012;201(3):180-185. PMID: 22945926.

*Calati R, Salvina Signorelli M, Balestri M, et al. Antidepressants in elderly: metaregression of double-blind, randomized clinical trials. J Affect Disord 2013;147(1-3):1-8. PMID: 23245467.

Cameron IM, Reid IC, MacGillivray SA. Efficacy and tolerability of antidepressants for sub-threshold depression and for mild major depressive disorder. J Affect Disord 2014;166:48-58. PMID: 25012410.

Carpenter DJ, Fong R, Kraus JE, et al. Meta-analysis of efficacy and treatment-emergent suicidality in adults by psychiatric indication and age subgroup following initiation of paroxetine therapy: a complete set of randomized placebo-controlled trials. J Clin Psychiatry 2011;72(11):1503-14. PMID: 21367354.

*Carter GC, Cantrell RA, Victoria Z, et al. Comprehensive review of factors implicated in the heterogeneity of response in depression. Depress Anxiety 2012;29(4):340-54. PMID: 22511365.

Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. Psychiatry Res 2011;187(3):441-53. PMID: 20846726.

Churchill R, Moore TH, Furukawa TA, et al. "Third wave" cognitive and behavioural therapies versus treatment as usual for depression. Cochrane Database Syst Rev 2013;10:Cd008705. PMID: 24142810.

Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for depression: a systematic review and meta-analysis. Depress Anxiety. 2013;30(11):1068-1083. PMID: 23922209.

Cuijpers P, Andersson G, Donker T, et al. Psychological treatment of depression: results of a series of meta-analyses. Nord J Psychiatry 2011;65(6):354-64. PMID: 21770842.

Cuijpers P, de Beurs DP, van Spijker BA, et al. The effects of psychotherapy for adult depression on suicidality and hopelessness: a systematic review and meta-analysis. J Affect Disord 2013;144(3):183-90. PMID: 22832172.

Cuijpers P, Dekker J, Hollon SD, et al. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis (Structured abstract). *J Clin Psychiatry*. Vol. 70; 2009:1219-1229.

Cuijpers P, Geraedts AS, van Oppen P, et al. Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatry 2011;168(6):581-92. PMID: 21362740.

Cuijpers P, Karyotaki E, Weitz E, et al. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. J Affect Disord 2014;159:118-26. PMID: 24679399.

Cuijpers P, Koole SL, van Dijke A, et al. Psychotherapy for subclinical depression: meta-analysis. Br J Psychiatry 2014;205(4):268-274. PMID: 25274315.

*Cuijpers P, Reynolds CF, 3rd, Donker T, et al. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. Depress Anxiety 2012;29(10):855-64. PMID: 22815247.

Cuijpers P, Sijbrandij M, Koole SL, et al. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. World Psychiatry 2013;12(2):137-48. PMID: 23737423.

Cuijpers P, Sijbrandij M, Koole SL, et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry 2014;13(1):56-67. PMID: 24497254.

Cuijpers P, Smit F, Bohlmeijer E, et al. Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. Br J Psychiatry 2010;196(3):173-8. PMID: 20194536.

Cuijpers P, Turner EH, Mohr DC, et al. Comparison of psychotherapies for adult depression to pill placebo control groups: a meta-analysis. Psychol Med 2014;44(4):685-95. PMID: 23552610.

Cuijpers P, van Straten A, Bohlmeijer E, et al. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. Psychol Med 2010;40(2):211-23. PMID: 19490745.

Cuijpers P, van Straten A, Hollon SD, et al. The contribution of active medication to combined treatments of psychotherapy and pharmacotherapy for adult depression: a meta-analysis. Acta Psychiatr Scand 2010;121(6):415-23. PMID: 19922522.

Cuijpers P, van Straten A, Schuurmans J, et al. Psychotherapy for chronic major depression and dysthymia: a meta-analysis. Clin Psychol Rev 2010;30(1):51-62. PMID: 19781837.

Danielsson L, Noras AM, Waern M, et al. Exercise in the treatment of major depression: a systematic review grading the quality of evidence. Physiother Theory Pract 2013;29(8):573-85. PMID: 23521569.

*Driessen E, Cuijpers P, de Maat SC, et al. The efficacy of short-term psychodynamic psychotherapy for depression: a meta-analysis. Clin Psychol Rev 2010;30(1):25-36. PMID: 19766369.

*Driessen E, Cuijpers P, Hollon SD, et al. Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. J Consult Clin Psychol 2010;78(5):668-80. PMID: 20873902.

Feng CY, Chu H, Chen CH, et al. The effect of cognitive behavioral group therapy for depression: a meta-analysis 2000-2010. Worldviews Evid Based Nurs 2012;9(1):2-17. PMID: 22221447.

Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010;303(1):47-53. PMID: 20051569.

*Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med 2011;155(11):772-85. PMID: 22147715.

Gibbons RD, Brown CH, Hur K, et al. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry 2012;69(6):580-7. PMID: 22309973.

Gibbons RD, Hur K, Brown CH, et al. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. Arch Gen Psychiatry 2012;69(6):572-9. PMID: 22393205.

*Gibiino S, Marsano A, Serretti A. Specificity profile of venlafaxine and sertraline in major depression: metaregression of double-blind, randomized clinical trials (Provisional abstract). *International Journal of Neuropsychopharmacology*. Vol. 17; 2014:1-8.

Glue P, Donovan MR, Kolluri S, et al. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. Aust N Z J Psychiatry 2010;44(8):697-705. PMID: 20636190.

Gould RL, Coulson MC, Howard RJ. Cognitive behavioral therapy for depression in older people: a meta-analysis and meta-regression of randomized controlled trials. J Am Geriatr Soc 2012;60(10):1817-30. PMID: 23003115.

Griffiths KM, Farrer L, Christensen H. The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials. Med J Aust 2010;192(11 Suppl):S4-11. PMID: 20528707.

Guidi J, Fava GA, Fava M, et al. Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. Psychol Med 2011;41(2):321-31. PMID: 20444307.

Hofmann SG, Sawyer AT, Witt AA, et al. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol 2010;78(2):169-83. PMID: 20350028.

Hunot V, Moore TH, Caldwell DM, et al. "Third wave" cognitive and behavioural therapies versus other psychological therapies for depression. Cochrane Database Syst Rev 2013;10:Cd008704. PMID: 24142844.

Jakobsen JC, Hansen JL, Simonsen E, et al. The effect of interpersonal psychotherapy and other psychodynamic therapies versus 'treatment as usual' in patients with major depressive disorder. PLoS One 2011;6(4):e19044. PMID: 21556370.

Jakobsen JC, Hansen JL, Simonsen E, et al. The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. J Affect Disord 2012;137(1-3):4-14. PMID: 21501877.

Jakobsen JC, Hansen JL, Simonsen S, et al. Effects of cognitive therapy versus interpersonal psychotherapy in patients with major depressive disorder: a systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. Psychol Med 2012;42(7):1343-57. PMID: 22051174.

Jakobsen JC, Hansen JL, Storebo OJ, et al. The effects of cognitive therapy versus 'no intervention' for major depressive disorder. PLoS One 2011;6(12):e28299. PMID: 22174786.

Jakobsen JC, Lindschou Hansen J, Storebo OJ, et al. The effects of cognitive therapy versus 'treatment as usual' in patients with major depressive disorder. PLoS One 2011;6(8):e22890. PMID: 21829664.

Josefsson T, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. Scand J Med Sci Sports. 2014;24(2):259-272. PMID: 23362828.

Kasper S, Corruble E, Hale A, et al. Antidepressant efficacy of agomelatine versus SSRI/SNRI: results from a pooled analysis of head-to-head studies without a placebo control. Int Clin Psychopharmacol 2013;28(1):12-9. PMID: 23023074.

Kennedy SH, Andersen HF, Thase ME. Escitalopram in the treatment of major depressive disorder: a meta-analysis (Structured abstract). *Current Medical Research and Opinion*. Vol. 25; 2009:161-175.

Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: a comprehensive meta-analysis. Clin Psychol Rev 2013;33(6):763-71. PMID: 23796855.

Kiosses DN, Leon AC, Arean PA. Psychosocial interventions for late-life major depression: evidence-based treatments, predictors of treatment outcomes, and moderators of treatment effects. Psychiatr Clin North Am 2011;34(2):377-401, viii. PMID: 21536164.

Krishna M, Honagodu A, Rajendra R, et al. A systematic review and meta-analysis of group psychotherapy for sub-clinical depression in older adults. Int J Geriatr Psychiatry 2013;28(9):881-8. PMID: 23147496.

Krishna M, Jauhari A, Lepping P, et al. Is group psychotherapy effective in older adults with depression? A systematic review. Int J Geriatr Psychiatry 2011;26(4):331-40. PMID: 20973096.

Kriston L, von Wolff A, Westphal A, et al. Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis. Depress Anxiety 2014;31(8):621-30. PMID: 24448972.

Krogh J, Nordentoft M, Sterne JA, Lawlor DA. The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. J Clin Psychiatry. 2011;72(4):529-538. PMID: 21034688.

Lee SY, Franchetti MK, Imanbayev A, et al. Non-pharmacological prevention of major depression among community-dwelling older adults: a systematic review of the efficacy of psychotherapy interventions. Arch Gerontol Geriatr 2012;55(3):522-9. PMID: 22483200.

Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: a meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry 2011;72(4):509-14. PMID: 21527126.

Lopes Rocha F, Fuzikawa C, Riera R, et al. Antidepressant combination for major depression in incomplete responders--a systematic review. J Affect Disord 2013;144(1-2):1-6. PMID: 22835845.

Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychol Med 2010;40(1):9-24. PMID: 19476688.

Machado M, Einarson TR. Comparison of SSRIs and SNRIs in major depressive disorder: a meta-analysis of head-to-head randomized clinical trials (Structured abstract). *Journal of Clinical Pharmacy and Therapeutics*. Vol. 35; 2010:177-188.

*Mancini M, Sheehan DV, Demyttenaere K, et al. Evaluation of the effect of duloxetine treatment on functioning as measured by the Sheehan disability scale: pooled analysis of data from six randomized, double-blind, placebo-controlled clinical studies. Int Clin Psychopharmacol 2012;27(6):298-309. PMID: 22954893.

Mura G, Moro MF, Patten SB, Carta MG. Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. CNS Spectr. 2014;19(6):496-508. PMID: 24589012.

Nieuwsma JA, Trivedi RB, McDuffie J, et al. Brief psychotherapy for depression: a systematic review and meta-analysis. Int J Psychiatry Med 2012;43(2):129-51. PMID: 22849036.

Okumura Y, Ichikura K. Efficacy and acceptability of group cognitive behavioral therapy for depression: a systematic review and meta-analysis. J Affect Disord 2014;164:155-64. PMID: 24856569.

Papakostas GI, Culpepper L, Fayyad RS, et al. Efficacy of desvenlafaxine 50 mg compared with placebo in patients with moderate or severe major depressive disorder: a pooled analysis of six randomized, double-blind, placebo-controlled studies (Provisional abstract). *Database of Abstracts of Reviews of Effects*; 2013:312-321.

Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. Clin Psychol Rev 2011;31(6):1032-40. PMID: 21802618.

Ramsberg J, Asseburg C, Henriksson M. Effectiveness and cost-effectiveness of antidepressants in primary care: a multiple treatment comparison meta-analysis and cost-effectiveness model. PLoS One 2012;7(8):e42003. PMID: 22876296.

Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. Clin Psychol Rev 2012;32(4):329-42. PMID: 22466510.

Rocha FL, Fuzikawa C, Riera R, et al. Combination of antidepressants in the treatment of major depressive disorder: a systematic review and meta-analysis. J Clin Psychopharmacol 2012;32(2):278-81. PMID: 22367652.

*Roshanaei-Moghaddam B, Pauly MC, Atkins DC, et al. Relative effects of CBT and pharmacotherapy in depression versus anxiety: is medication somewhat better for depression, and CBT somewhat better for anxiety? Depress Anxiety 2011;28(7):560-7. PMID: 21608087.

Rubenstein LV, Williams JW, Jr., Danz M, Shekelle P, Suttorp M, Johnsen B. VA Evidence-based Synthesis Program Reports. *Determining Key Features of Effective Depression Interventions.* Washington (DC): Department of Veterans Affairs (US); 2009.

Samad Z, Brealey S, Gilbody S. The effectiveness of behavioural therapy for the treatment of depression in older adults: a meta-analysis. Int J Geriatr Psychiatry 2011;26(12):1211-20. PMID: 21308789.

Schueler YB, Koesters M, Wieseler B, et al. A systematic review of duloxetine and venlafaxine in major depression, including unpublished data. Acta Psychiatr Scand 2011;123(4):247-65. PMID: 20831742.

Shinohara K, Honyashiki M, Imai H, et al. Behavioural therapies versus other psychological therapies for depression. Cochrane Database Syst Rev 2013;10:Cd008696. PMID: 24129886.

Silveira H, Moraes H, Oliveira N, Coutinho ES, Laks J, Deslandes A. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. Neuropsychobiology. 2013;67(2):61-68. PMID: 23295766.

So M, Yamaguchi S, Hashimoto S, et al. Is computerised CBT really helpful for adult depression?-A meta-analytic re-evaluation of CCBT for adult depression in terms of clinical implementation and methodological validity. BMC Psychiatry 2013;13:113. PMID: 23587347.

*Soares CN, Fayyad RS, Guico-Pabia CJ. Early improvement in depressive symptoms with desvenlafaxine 50 mg/d as a predictor of treatment success in patients with major depressive disorder. J Clin Psychopharmacol. 2014;34(1):57-65 PMID: 24346751

Spielmans GI, Berman MI, Usitalo AN. Psychotherapy versus second-generation antidepressants in the treatment of depression: a meta-analysis. J Nerv Ment Dis 2011;199(3):142-9. PMID: 21346483.

Spijker J, van Straten A, Bockting CL, et al. Psychotherapy, antidepressants, and their combination for chronic major depressive disorder: a systematic review. Can J Psychiatry 2013;58(7):386-92. PMID: 23870720.

Tedeschini E, Levkovitz Y, Iovieno N, et al. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. J Clin Psychiatry 2011;72(12):1660-8. PMID: 22244025.

*Thota AB, Sipe TA, Byard GJ, et al. Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. Am J Prev Med 2012;42(5):525-38. PMID: 22516495.

Trivedi RB, Nieuwsma JA, Williams JW, Jr. Examination of the utility of psychotherapy for patients with treatment resistant depression: a systematic review. J Gen Intern Med 2011;26(6):643-50. PMID: 21184287.

van Hees ML, Rotter T, Ellermann T, et al. The effectiveness of individual interpersonal psychotherapy as a treatment for major depressive disorder in adult outpatients: a systematic review. BMC Psychiatry 2013;13:22. PMID: 23312024.

*von Wolff A, Holzel LP, Westphal A, et al. Combination of pharmacotherapy and psychotherapy in the treatment of chronic depression: a systematic review and meta-analysis. BMC Psychiatry 2012;12:61. PMID: 22694751.

von Wolff A, Holzel LP, Westphal A, et al. Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis. J Affect Disord 2013;144(1-2):7-15. PMID: 22963896.

Woltmann E, Grogan-Kaylor A, Perron B, et al. Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: systematic review and meta-analysis. Am J Psychiatry 2012;169(8):790-804. PMID: 22772364

Type 2 Diabetes (114)

Abdul-Ghani MA, Williams K, Kanat M, et al. Insulin vs GLP-1 analogues in poorly controlled Type 2 diabetic subjects on oral therapy: a meta-analysis. J Endocrinol Invest 2013;36(3):168-73. PMID: 22522662.

Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013;97(3):505-16. PMID: 23364002.

Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. Clin Ther 2012;34(6):1247-1258.e22. PMID: 22608780.

Attridge M, Creamer J, Ramsden M, et al. Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2014.

Avery L, Flynn D, van Wersch A, et al. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. Diabetes Care 2012;35(12):2681-9. PMID: 23173137.

Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154(9):602-13. PMID: 21403054.

Bosetti C, Rosato V, Buniato D, Zambon A, La Vecchia C, Corrao G. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. Oncologist. 2013;18(2):148-156. PMID: 23345544.

Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med 2012;9(4):e1001204. PMID: 22509138.

Castaneda-Gonzalez LM, Bacardi Gascon M, Jimenez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. Nutr Hosp 2011;26(6):1270-6. PMID: 22411372.

Chapell R, Gould AL, Alexander CM. Baseline differences in A1C explain apparent differences in efficacy of sitagliptin, rosiglitazone and pioglitazone. Diabetes Obes Metab 2009;11(11):1009-16. PMID: 19614948.

Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. Diabetes Care 2011;34(5):1228-37. PMID: 21525503.

Cleveringa FG, Gorter KJ, van den Donk M, et al. Computerized decision support systems in primary care for type 2 diabetes patients only improve patients' outcomes when combined with feedback on performance and case management: a systematic review. Diabetes Technol Ther 2013;15(2):180-92. PMID: 23360424.

Col NF, Ochs L, Springmann V, et al. Metformin and breast cancer risk: a meta-analysis and critical literature review. Breast Cancer Res Treat 2012;135(3):639-46. PMID: 22847511.

Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. Cmaj. 2012;184(12):E675-683. PMID: 22761478.

Colmers IN, Bowker SL, Tjosvold LA, et al. Insulin use and cancer risk in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab 2012;38(6):485-506. PMID: 23159131.

Cramer H, Lauche R, Haller H, et al. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. Int J Cardiol 2014;173(2):170-83. PMID: 24636547.

Decensi A, Puntoni M, Goodwin P, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2010;3(11):1451-1461. PMID: 20947488.

Dixon JB, Murphy DK, Segel JE, et al. Impact of laparoscopic adjustable gastric banding on type 2 diabetes. Obes Rev 2012;13(1):57-67. PMID: 21880108.

Dong JY, Zhang ZL, Wang PY, et al. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. Br J Nutr 2013;110(5):781-9. PMID: 23829939.

Egginton JS, Ridgeway JL, Shah ND, et al. Care management for Type 2 diabetes in the United States: a systematic review and meta-analysis. BMC Health Serv Res 2012;12:72. PMID: 22439920.

*Esposito K, Chiodini P, Bellastella G, et al. Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. Diabetes Obes Metab 2012;14(3):228-33. PMID: 21958121.

*Esposito K, Cozzolino D, Bellastella G, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2011;13(7):594-603. PMID: 21320267.

*Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010;86(1):44-57. PMID: 20616619.

Fonseca V, Gill J, Zhou R, et al. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes Obes Metab 2011;13(9):814-22. PMID: 21481127.

Forst T, Hanefeld M, Jacob S, et al. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: a systematic review and meta-analysis of observational studies. Diab Vasc Dis Res 2013;10(4):302-14. PMID: 23291340.

Franciosi M, Lucisano G, Lapice E, et al. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013;8(8):e71583. PMID: 23936520.

Fried M, Ribaric G, Buchwald JN, et al. Metabolic surgery for the treatment of type 2 diabetes in patients with BMI <35 kg/m2: an integrative review of early studies. Obes Surg 2010;20(6):776-90. PMID: 20333558.

Gill RS, Birch DW, Shi X, et al. Sleeve gastrectomy and type 2 diabetes mellitus: a systematic review. Surg Obes Relat Dis 2010;6(6):707-13. PMID: 20947447.

Goossen K, Graber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 2012;14(12):1061-72. PMID: 22519906.

*Groop PH, Del Prato S, Taskinen MR, et al. Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. Diabetes Obes Metab 2014;16(6):560-8. PMID: 24612167.

Gross JL, Kramer CK, Leitao CB, et al. Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 2011;154(10):672-9. PMID: 21576535.

*Gucciardi E, Chan VW, Manuel L, et al. A systematic literature review of diabetes self-management education features to improve diabetes education in women of Black African/Caribbean and Hispanic/Latin American ethnicity. Patient Educ Couns 2013;92(2):235-45. PMID: 23566428.

Guo X, Liu X, Wang M, et al. The effects of bariatric procedures versus medical therapy for obese patients with type 2 diabetes: meta-analysis of randomized controlled trials. Biomed Res Int 2013;2013:410609. PMID: 23971035.

Han S, Iglay K, Davies MJ, et al. Glycemic effectiveness and medication adherence with fixed-dose combination or coadministered dual therapy of antihyperglycemic regimens: a meta-analysis. Curr Med Res Opin 2012;28(6):969-77. PMID: 22494018.

*He S, Tang YH, Zhao G, et al. Pioglitazone prescription increases risk of bladder cancer in patients with type 2 diabetes: an updated meta-analysis. Tumour Biol 2014;35(3):2095-102. PMID: 24092576.

Hemmingsen B, Christensen LL, Wetterslev J, et al. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. Bmj 2012;344:e1771. PMID: 22517929.

Hemmingsen B, Schroll JB, Lund SS, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. Cochrane Database Syst Rev 2013;4:Cd009008. PMID: 23633364.

Hernandez AV, Usmani A, Rajamanickam A, et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011;11(2):115-28. PMID: 21294599.

Home PD, Fritsche A, Schinzel S, et al. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. Diabetes Obes Metab 2010;12(9):772-9. PMID: 20649629.

Hovanec N, Sawant A, Overend TJ, et al. Resistance training and older adults with type 2 diabetes mellitus: strength of the evidence. J Aging Res 2012;2012:284635. PMID: 22988507.

Janghorbani M, Dehghani M, Salehi-Marzijarani M. Systematic review and meta-analysis of insulin therapy and risk of cancer. Horm Cancer 2012;3(4):137-46. PMID: 22528451.

*Johansen OE, Neubacher D, von Eynatten M, et al. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. Cardiovasc Diabetol 2012;11:3. PMID: 22234149.

Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. Bmj 2012;344:e1369. PMID: 22411919.

Kawalec P, Mikrut A, Lopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Res Rev 2014;30(4):269-83. PMID: 24829965.

*Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2013;1(1):28-34. PMID: 24622264.

*Lamanna C, Monami M, Marchionni N, et al. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2011;13(3):221-8. PMID: 21205121.

*Lapane KL, Yang S, Brown MJ, et al. Sulfonylureas and risk of falls and fractures: a systematic review. Drugs Aging 2013;30(7):527-47. PMID: 23609875.

Lee MS, Choi TY, Lim HJ, et al. Tai chi for management of type 2 diabetes mellitus: a systematic review. Chin J Integr Med 2011;17(10):789-93. PMID: 21805298.

Lee NJ, Norris SL, Thakurta S. Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. Ann Fam Med 2010;8(6):542-9. PMID: 21060125.

Li C, Xia J, Zhang G, et al. Nateglinide versus repaglinide for type 2 diabetes mellitus in China. Acta Diabetol 2009;46(4):325-33. PMID: 19183841.

Li JF, Lai DD, Ni B, et al. Comparison of laparoscopic Roux-en-Y gastric bypass with laparoscopic sleeve gastrectomy for morbid obesity or type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Can J Surg 2013;56(6):E158-64. PMID: 24284156.

Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. Bmj. 2014;348:g2366. PMID: 24736555.

Li Q, Chen L, Yang Z, et al. Metabolic effects of bariatric surgery in type 2 diabetic patients with body mass index < 35 kg/m2. Diabetes Obes Metab 2012;14(3):262-70. PMID: 22051116.

Liang X, Wang Q, Yang X, et al. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabet Med 2011;28(4):455-63. PMID: 21392066.

Liu Q, Li S, Quan H, Li J. Vitamin B12 status in metformin treated patients: systematic review. PLoS One. 2014;9(6):e100379. PMID: 24959880.

Liu SC, Tu YK, Chien MN, et al. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab 2012;14(9):810-20. PMID: 22486990.

Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. Bmj 2011;342:d1309. PMID: 21415101.

MacLeod SF, Terada T, Chahal BS, et al. Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using continuous glucose monitoring. Diabetes Metab Res Rev 2013;29(8):593-603. PMID: 24038928.

Mannucci E, Monami M, Lamanna C, et al. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2009;19(9):604-12. PMID: 19427768.

McGinley SK, Armstrong MJ, Boule NG, et al. Effects of exercise training using resistance bands on glycaemic control and strength in type 2 diabetes mellitus: a meta-analysis of randomised controlled trials. Acta Diabetol 2014. PMID: 24845604.

McIntosh B, Cameron C, Singh SR, et al. Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis. Open Med 2012;6(2):e62-74. PMID: 23696771.

Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. Diabetes Care. 2011;34(11):2474-2476. PMID: 22025784.

Monami M, Ahren B, Dicembrini I, et al. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15(2):112-20. PMID: 22925682.

Monami M, Dicembrini I, Mannucci E. Thiazolidinediones and cancer: results of a meta-analysis of randomized clinical trials. Acta Diabetol 2014;51(1):91-101. PMID: 23851465.

Monami M, Dicembrini I, Nardini C, et al. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16(1):38-47. PMID: 23829656.

Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16(5):457-66. PMID: 24320621.

Musso G, Gambino R, Cassader M, et al. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 2012;44(4):375-93. PMID: 21495788.

Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med. 2015;10(1):93-102. PMID: 25502588.

Oliveira C, Simoes M, Carvalho J, et al. Combined exercise for people with type 2 diabetes mellitus: a systematic review. Diabetes Res Clin Pract 2012;98(2):187-98. PMID: 22981711.

*Parikh M, Issa R, Vieira D, et al. Role of bariatric surgery as treatment for type 2 diabetes in patients who do not meet current NIH criteria: a systematic review and meta-analysis. J Am Coll Surg 2013;217(3):527-32. PMID: 23890843.

Phung OJ, Scholle JM, Talwar M, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. Jama 2010;303(14):1410-8. PMID: 20388897.

Phung OJ, Schwartzman E, Allen RW, et al. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med 2013;30(10):1160-71. PMID: 23663156.

Phung OJ, Sobieraj DM, Engel SS, et al. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 2014;16(5):410-7. PMID: 24205921.

Picot J, Jones J, Colquitt JL, et al. Weight loss surgery for mild to moderate obesity: a systematic review and economic evaluation. Obes Surg 2012;22(9):1496-506. PMID: 22926715.

Poolsup N, Suksomboon N, Setwiwattanakul W. Efficacy of various antidiabetic agents as add-on treatments to metformin in type 2 diabetes mellitus: systematic review and meta-analysis. ISRN Endocrinol 2012;2012:798146. PMID: 22619731.

Ribaric G, Buchwald JN, McGlennon TW. Diabetes and weight in comparative studies of bariatric surgery vs conventional medical therapy: a systematic review and meta-analysis. Obes Surg 2014;24(3):437-55. PMID: 24374842.

Ricci-Cabello I, Ruiz-Perez I, Rojas-Garcia A, et al. Improving diabetes care in rural areas: a systematic review and meta-analysis of quality improvement interventions in OECD countries. PLoS One 2013;8(12):e84464. PMID: 24367662.

Rizos EC, Ntzani EE, Papanas N, et al. Combination therapies of DPP4 inhibitors and GLP1 analogues with insulin in type 2 diabetic patients: a systematic review. Curr Vasc Pharmacol. 2013;11(6):992-1000. PMID: 22724475.

Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010(1):Cd002967. PMID: 20091535.

Schellenberg ES, Dryden DM, Vandermeer B, et al. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159(8):543-51. PMID: 24126648.

Schopman JE, Simon AC, Hoefnagel SJ, et al. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. Diabetes Metab Res Rev 2014;30(1):11-22. PMID: 24030920.

*Schweizer A, Dejager S, Foley JE, et al. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population. Diabetes Obes Metab 2010;12(6):485-94. PMID: 20518804.

Schwingshackl L, Hoffmann G. Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis. Br J Nutr 2014;111(12):2047-58. PMID: 24666665.

Schwingshackl L, Missbach B, Dias S, et al. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetologia 2014;57(9):1789-97. PMID: 24996616.

Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care 2010;33(8):1859-64. PMID: 20484130.

Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011(10):Cd006423. PMID: 21975753.

Singh S, Singh H, Singh PP, et al. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2013;22(12):2258-68. PMID: 24042261.

Singh S, Singh PP, Singh AG, et al. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. Am J Gastroenterol 2013;108(6):881-91; quiz 892. PMID: 23381014.

Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2011;13(2):169-80. PMID: 21199269.

Soranna D, Scotti L, Zambon A, et al. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. Oncologist. 2012;17(6):813-822. PMID: 22643536.

Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports Med 2010;40(5):397-415. PMID: 20433212.

Sun YN, Zhou Y, Chen X, et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. BMJ Open 2014;4(4):e004619. PMID: 24710132.

Thakkar B, Aronis KN, Vamvini MT, et al. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism 2013;62(7):922-34. PMID: 23419783.

Tieu J, Coat S, Hague W, et al. Oral anti-diabetic agents for women with pre-existing diabetes mellitus/impaired glucose tolerance or previous gestational diabetes mellitus. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2010.

Umpierre D, Ribeiro PA, Schaan BD, et al. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. Diabetologia 2013;56(2):242-51. PMID: 23160642.

Vaes AW, Cheung A, Atakhorrami M, et al. Effect of 'activity monitor-based' counseling on physical activity and health-related outcomes in patients with chronic diseases: A systematic review and meta-analysis. Ann Med 2013;45(5-6):397-412. PMID: 23952917.

van Vugt M, de Wit M, Cleijne WH, et al. Use of behavioral change techniques in web-based self-management programs for type 2 diabetes patients: systematic review. J Med Internet Res 2013;15(12):e279. PMID: 24334230.

Varas-Lorenzo C, Margulis AV, Pladevall M, et al. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. BMC Cardiovasc Disord 2014;14:129. PMID: 25260374.

Vilsboll T, Christensen M, Junker AE, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. Bmj 2012;344:d7771. PMID: 22236411.

*Wang GF, Yan YX, Xu N, et al. Predictive Factors of Type 2 Diabetes Mellitus Remission Following Bariatric Surgery: a Meta-analysis. Obes Surg 2015;25(2):199-208. PMID: 25103403.

Wang S, Li P, Sun XF, et al. Comparison between laparoscopic sleeve gastrectomy and laparoscopic adjustable gastric banding for morbid obesity: a meta-analysis. Obes Surg 2013;23(7):980-6. PMID: 23604584.

Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 2014;106(1):19-26. PMID: 24837144.

Waugh N, Cummins E, Royle P, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol Assess 2010;14(36):1-248. PMID: 20646668.

Wu Y, Liu HB, Shi XF, et al. Conventional hypoglycaemic agents and the risk of lung cancer in patients with diabetes: a meta-analysis. PLoS One 2014;9(6):e99577. PMID: 24924771.

Yan JH, Gu WJ, Pan L. Lack of evidence on Tai Chi-related effects in patients with type 2 diabetes mellitus: a meta-analysis. Exp Clin Endocrinol Diabetes 2013;121(5):266-71. PMID: 23450333.

Yang Z, Scott CA, Mao C, et al. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. Sports Med 2014;44(4):487-99. PMID: 24297743.

Yin J, Deng H, Qin S, et al. Comparison of repaglinide and metformin versus metformin alone for type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2014;105(3):e10-5. PMID: 25005849.

Yip S, Plank LD, Murphy R. Gastric bypass and sleeve gastrectomy for type 2 diabetes: a systematic review and meta-analysis of outcomes. Obes Surg 2013;23(12):1994-2003. PMID: 23955521.

Zhang F, Xiang H, Fan Y, et al. The effects of sulfonylureas plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes: a meta-analysis of randomized controlled trials. Endocrine 2013;44(3):648-58. PMID: 23657947.

Zhang Q, Dou J, Lu J. Combinational therapy with metformin and sodium-glucose cotransporter inhibitors in management of type 2 diabetes: systematic review and meta-analyses. Diabetes Res Clin Pract 2014;105(3):313-21. PMID: 25015317.

Zhang Y, Hong J, Chi J, et al. Head-to-head comparison of dipeptidyl peptidase-IV inhibitors and sulfonylureas - a meta-analysis from randomized clinical trials. Diabetes Metab Res Rev 2014;30(3):241-56. PMID: 24123720.

Zhou J, Zhang L, Liu H, et al. Tai Chi for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2012.

Zhu Z, Shen Z, Lu Y, Zhong S, Xu C. Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract. 2012;98(1):159-163. PMID: 22705039.

Zintzaras E, Miligkos M, Ziakas P, et al. Assessment of the relative effectiveness and tolerability of treatments of type 2 diabetes mellitus: a network meta-analysis. Clin Ther 2014;36(10):1443-53.e9. PMID: 25109773

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Avouac J, Vicaut E, Bardin T, Richette P. Efficacy of joint lavage in knee osteoarthritis: meta-analysis of randomized controlled studies. Rheumatology (Oxford). 2010;49(2):334-340. PMID: 19955221.

Bannuru RR, Natov NS, Dasi UR, et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011;19(6):611-9. PMID: 21443958.

Bernardy K, Fuber N, Kollner V, et al. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials. J Rheumatol 2010;37(10):1991-2005. PMID: 20682676.

Bernardy K, Klose P, Busch AJ, et al. Cognitive behavioural therapies for fibromyalgia. Cochrane Database Syst Rev 2013;9:Cd009796. PMID: 24018611.

Bidonde J, Busch AJ, Webber SC, et al. Aquatic exercise training for fibromyalgia. Cochrane Database Syst Rev 2014;10:Cd011336. PMID: 25350761.

Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2013;12:Cd010884. PMID: 24362925.

Cao H, Li X, Han M, et al. Acupoint stimulation for fibromyalgia: a systematic review of randomized controlled trials. Evid Based Complement Alternat Med 2013;2013:362831. PMID: 24454493.

Cao H, Liu J, Lewith GT. Traditional Chinese Medicine for treatment of fibromyalgia: a systematic review of randomized controlled trials. J Altern Complement Med 2010;16(4):397-409. PMID: 20423209.

*Cawston H, Davie A, Paget MA, et al. Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain. Eur Spine J 2013;22(9):1996-2009. PMID: 23686477.

Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine (Phila Pa 1976). 2009;34(10):1078-1093. PMID: 19363456.

Choy E, Marshall D, Gabriel ZL, et al. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Semin Arthritis Rheum 2011;41(3):335-45.e6. PMID: 21868065.

Clarke CL, Ryan CG, Martin DJ. Pain neurophysiology education for the management of individuals with chronic low back pain: systematic review and meta-analysis. Man Ther 2011;16(6):544-9. PMID: 21705261.

Cramer H, Lauche R, Haller H, et al. A systematic review and meta-analysis of yoga for low back pain. Clin J Pain 2013;29(5):450-60. PMID: 23246998.

Deare JC, Zheng Z, Xue CC, et al. Acupuncture for treating fibromyalgia. Cochrane Database Syst Rev 2013;5:Cd007070. PMID: 23728665.

Derry S, Gill D, Phillips T, et al. Milnacipran for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012;3:Cd008244. PMID: 22419330.

Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2012;9:Cd007400. PMID: 22972108.

Ernst E. Chiropractic treatment for fibromyalgia: a systematic review. Clin Rheumatol 2009;28(10):1175-8. PMID: 19544042.

Falco FJ, Manchikanti L, Datta S, et al. An update of the effectiveness of therapeutic lumbar facet joint interventions. Pain Physician 2012;15(6):E909-53. PMID: 23159980.

Ferreira ML, Smeets RJ, Kamper SJ, et al. Can we explain heterogeneity among randomized clinical trials of exercise for chronic back pain? A meta-regression analysis of randomized controlled trials. Phys Ther 2010;90(10):1383-403. PMID: 20671101.

Fersum KV, Dankaerts W, O'Sullivan PB, et al. Integration of subclassification strategies in randomised controlled clinical trials evaluating manual therapy treatment and exercise therapy for non-specific chronic low back pain: a systematic review. Br J Sports Med 2010;44(14):1054-62. PMID: 19996331.

Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 2015;1:Cd004376. PMID: 25569281.

Glombiewski JA, Bernardy K, Hauser W. Efficacy of EMG- and EEG-Biofeedback in Fibromyalgia Syndrome: A Meta-Analysis and a Systematic Review of Randomized Controlled Trials. Evid Based Complement Alternat Med 2013;2013:962741. PMID: 24082911.

Glombiewski JA, Sawyer AT, Gutermann J, et al. Psychological treatments for fibromyalgia: a meta-analysis. Pain 2010;151(2):280-95. PMID: 20727679.

Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther 2010;12(3):R79. PMID: 20459730.

Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 2010;11(6):505-21. PMID: 20418173.

Hauser W, Petzke F, Uceyler N, et al. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology (Oxford) 2011;50(3):532-43. PMID: 21078630.

*Hauser W, Urrutia G, Tort S, et al. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst Rev 2013;1:Cd010292. PMID: 23440848.

Hauser W, Wolfe F, Tolle T, et al. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. CNS Drugs 2012;26(4):297-307. PMID: 22452526.

Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. Cochrane Database Syst Rev 2010(7):Cd002014. PMID: 20614428.

Holtzman S, Beggs RT. Yoga for chronic low back pain: a meta-analysis of randomized controlled trials. Pain Res Manag 2013;18(5):267-72. PMID: 23894731.

Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy. 2013;29(12):2037-2048. PMID: 24286802.

Lam M, Galvin R, Curry P. Effectiveness of acupuncture for nonspecific chronic low back pain: a systematic review and meta-analysis. Spine (Phila Pa 1976) 2013;38(24):2124-38. PMID: 24026151.

Langhorst J, Klose P, Dobos GJ, et al. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. Rheumatol Int 2013;33(1):193-207. PMID: 22350253.

Langhorst J, Klose P, Musial F, et al. Efficacy of acupuncture in fibromyalgia syndrome--a systematic review with a meta-analysis of controlled clinical trials. Rheumatology (Oxford) 2010;49(4):778-88. PMID: 20100789.

Lauche R, Cramer H, Dobos G, et al. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. J Psychosom Res 2013;75(6):500-10. PMID: 24290038.

Lima TB, Dias JM, Mazuquin BF, et al. The effectiveness of aquatic physical therapy in the treatment of fibromyalgia: a systematic review with meta-analysis. Clin Rehabil 2013;27(10):892-908. PMID: 23818412.

Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014;1:Cd007115. PMID: 24385423.

Meng XG, Yue SW. Efficacy of Aerobic Exercise for Treatment of Chronic Low Back Pain: A Meta-Analysis. Am J Phys Med Rehabil 2014. PMID: 25299528.

Mist SD, Firestone KA, Jones KD. Complementary and alternative exercise for fibromyalgia: a meta-analysis. J Pain Res 2013;6:247-60. PMID: 23569397.

Miyamoto GC, Costa LO, Cabral CM. Efficacy of the Pilates method for pain and disability in patients with chronic nonspecific low back pain: a systematic review with meta-analysis. Braz J Phys Ther 2013;17(6):517-32. PMID: 24346291.

Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012;12:Cd008242. PMID: 23235657.

Moore RA, Straube S, Wiffen Philip J, et al. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2009.

Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014;4:Cd007938. PMID: 24771480.

Nuesch E, Hauser W, Bernardy K, et al. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis 2013;72(6):955-62. PMID: 22739992.

Orrock PJ, Myers SP. Osteopathic intervention in chronic non-specific low back pain: a systematic review. BMC Musculoskelet Disord 2013;14:129. PMID: 23570655.

Parr AT, Manchikanti L, Hameed H, et al. Caudal epidural injections in the management of chronic low back pain: a systematic appraisal of the literature. Pain Physician 2012;15(3):E159-98. PMID: 22622911.

Pereira LM, Obara K, Dias JM, et al. Comparing the Pilates method with no exercise or lumbar stabilization for pain and functionality in patients with chronic low back pain: systematic review and meta-analysis. Clin Rehabil 2012;26(1):10-20. PMID: 21856719.

Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. Eur J Pain 2014;18(8):1067-80. PMID: 25139817.

Roskell NS, Beard SM, Zhao Y, et al. A meta-analysis of pain response in the treatment of fibromyalgia. Pain Pract 2011;11(6):516-27. PMID: 21199320.

Rubinstein SM, van Middelkoop M, Assendelft WJ, et al. Spinal manipulative therapy for chronic low-back pain. Cochrane Database Syst Rev 2011(2):Cd008112. PMID: 21328304.

Rubinstein SM, van Middelkoop M, Kuijpers T, et al. A systematic review on the effectiveness of complementary and alternative medicine for chronic non-specific low-back pain. Eur Spine J 2010;19(8):1213-28. PMID: 20229280.

Schaafsma FG, Whelan K, van der Beek AJ, et al. Physical conditioning as part of a return to work strategy to reduce sickness absence for workers with back pain. Cochrane Database Syst Rev 2013;8:Cd001822. PMID: 23990391.

Searle A, Spink M, Ho A, et al. Exercise interventions for the treatment of chronic low back pain: A systematic review and meta-analysis of randomised controlled trials. Clin Rehabil 2015. PMID: 25681408.

Smith TO, King JJ, Hing CB. The effectiveness of proprioceptive-based exercise for osteoarthritis of the knee: a systematic review and meta-analysis. Rheumatol Int. 2012;32(11):3339-3351. PMID: 22821333.

Standaert CJ, Friedly J, Erwin MW, et al. Comparative effectiveness of exercise, acupuncture, and spinal manipulation for low back pain. Spine (Phila Pa 1976) 2011;36(21 Suppl):S120-30. PMID: 21952184.

Straube S, Derry S, Moore RA, et al. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology (Oxford) 2010;49(4):706-15. PMID: 20056767.

Tzellos TG, Toulis KA, Goulis DG, et al. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. J Clin Pharm Ther 2010;35(6):639-56. PMID: 21054455.

Uceyler N, Sommer C, Walitt B, et al. Anticonvulsants for fibromyalgia. Cochrane Database Syst Rev 2013;10:Cd010782. PMID: 24129853.

van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. Eur Spine J 2011;20(1):19-39. PMID: 20640863.

Veehof MM, Oskam MJ, Schreurs KM, et al. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. Pain 2011;152(3):533-42. PMID: 21251756.

Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;172(19):1444-53. PMID: 22965186.

Wallis JA, Taylor NF. Pre-operative interventions (non-surgical and non-pharmacological) for patients with hip or knee osteoarthritis awaiting joint replacement surgery--a systematic review and meta-analysis. Osteoarthritis Cartilage. 2011;19(12):1381-1395. PMID: 21959097.

Wang XQ, Zheng JJ, Yu ZW, et al. A meta-analysis of core stability exercise versus general exercise for chronic low back pain. PLoS One 2012;7(12):e52082. PMID: 23284879.

Ward L, Stebbings S, Cherkin D, et al. Yoga for functional ability, pain and psychosocial outcomes in musculoskeletal conditions: a systematic review and meta-analysis. Musculoskeletal Care 2013;11(4):203-17. PMID: 23300142.

*Waterschoot FP, Dijkstra PU, Hollak N, et al. Dose or content? Effectiveness of pain rehabilitation programs for patients with chronic low back pain: a systematic review. Pain 2014;155(1):179-89. PMID: 24135435.

Wells C, Kolt GS, Marshall P, et al. The effectiveness of Pilates exercise in people with chronic low back pain: a systematic review. PLoS One 2014;9(7):e100402. PMID: 24984069.

Xu M, Yan S, Yin X, et al. Acupuncture for chronic low back pain in long-term follow-up: a meta-analysis of 13 randomized controlled trials. Am J Chin Med 2013;41(1):1-19. PMID: 23336503.

Yang B, Yi G, Hong W, et al. Efficacy of acupuncture on fibromyalgia syndrome: a meta-analysis. J Tradit Chin Med 2014;34(4):381-91. PMID: 25185355.