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Reporting of Sex Effects by Systematic Reviews on Interventions for Depression, Diabetes, and Chronic Pain

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Abstract

Systematic reviews (SRs) have the potential to contribute uniquely to the evaluation of sex and gender differences (termed “sex effects”). This article describes the reporting of sex effects by SRs on interventions for depression, type 2 diabetes mellitus, and chronic pain conditions (chronic low back pain, knee osteoarthritis, and fibromyalgia). It includes SRs published since 1 October 2009 that evaluate medications, behavioral interventions, exercise, quality improvement, and some condition-specific treatments. The reporting of sex effects by primary randomized, controlled trials is also examined. Of 313 eligible SRs (86 for depression, 159 for type 2 diabetes mellitus, and 68 for chronic pain), few (n = 29) reported sex effects. Most SRs reporting sex effects used metaregression, whereas 9 SRs used subgroup analysis or individual-patient data meta-analysis. The proportion of SRs reporting the sex distribution of primary studies varied from a low of 31% (n = 8) for low back pain to a high of 68% (n = 23) for fibromyalgia. Primary randomized, controlled trials also infrequently reported sex effects, and most lacked an adequate sample size to examine them. Therefore, all SRs should report the proportion of women enrolled in primary studies and evaluate sex effects using appropriate methods whenever power is adequate.

Differences in disease prevalence, clinical manifestations, and health outcomes exist between men and women. Sources for this variation range from biological differentiation at the cellular level to behavioral differences influenced by societal gender norms. Typically, biologically based differences between men and women are called “sex differences,” whereas “gender differences” describe health differences related, at least in part, to societal constructs of gender (1–3). For example, biological events unique to women, such as pregnancy and menopause, are probably associated with sex differences in occurrence of certain conditions or in response to some medical therapies (4–8). Gender differences probably exist in health-related perceptions and behaviors for women and men with medical conditions that are prevalent for both sexes (for example, heart disease and chronic pain) (9–16). Although sex and gender differences are theoretically distinct, they remain difficult to disentangle when differences between men and women in health outcomes and treatment effectiveness are being examined. For this reason, and for brevity, we hereafter refer to sex and gender differences collectively as “sex effects.”

In the past 2 decades, recognition of the importance of sex effects for health outcomes and treatment heterogeneity has been growing. Beginning in 1993, the National Institutes of Health has issued policies requiring the inclusion of women and minorities in all clinical research and trial designs with valid analysis of sex effects or differences between racial and ethnic groups (17, 18). Since then, the inclusion of women in clinical trials has increased (19, 20), and sex effects have been identified for medications, such as nicotine replacement therapy, analgesics, and aspirin (13, 14, 21). Recently, sex effects in adverse reactions led to sex-specific dosage recommendations for a widely used sedative (7). Despite this progress, representation of women in clinical studies remains inadequate for many conditions (22). Further, published clinical trials infrequently report sex effects or discuss the appropriateness of sex-specific analyses (19, 20, 23). To advance the clinical evidence base and improve health outcomes for women, clinical research must include adequate numbers of women, appropriately conduct sex-specific analyses, and consistently report sex effects.

Systematic reviews (SRs) are a key source of information for clinicians, researchers, and guideline panels. By synthesizing the overall body of evidence for key clinical and research questions, SRs could potentially make a unique contribution to the evaluation of sex effects. To our knowledge, however, the reporting of sex effects by SRs has not been previously examined.

Here, we use evidence mapping to systematically evaluate the reporting of sex effects by SRs examining a diverse set of interventions for chronic conditions common to women (that is, depression, diabetes, and chronic pain). Evidence mapping is an emerging approach that describes key characteristics of studies for a broad area of medicine (24–26). Our evidence map addresses the volume and characteristics of eligible SRs, including the representation of women in primary studies, whether and how reviews reported sex effects, and findings about sex effects.

Methods

This work was part of a larger report for the Veterans Health Administration (VHA) Evidence-based Synthesis Program (ESP). The complete technical report is available online (www.hsrd.research.va.gov/publications/esp) and includes additional information on our methods. We focused on SRs to determine the reporting of sex effects, provide high-level information about the volume of current clinical evidence, and summarize information about actual sex effects.

Prioritization of Conditions for Inclusion

We used forced-ranking prioritization (27) with our VHA stakeholders to determine our conditions of interest. These stakeholders included representatives from the Health Services Research & Development Center for the Study of Healthcare Innovation, Implementation and Policy; Health Services Research & Development Women's Health Research Network; Women's Health Research in the Office of Research & Development; Women's Health Services; and Mental Health Services. We initially selected 34 conditions (Appendix Table 1, available at www.annals.org) based on disease prevalence in women, disease burden in women, availability and breadth of effective treatments for men or women, and women

veterans' priorities for gender-specific care. Stakeholders ranked this initial set of conditions, discussed the rankings, and reranked conditions that initially received intermediate priority rankings. After 2 rounds of iterative prioritization, the following conditions were selected: depressive disorders, type 2 diabetes mellitus, and chronic pain (that is, chronic low back pain, fibromyalgia, and chronic knee pain due to osteoarthritis).

Data Sources and Searches

In collaboration with an expert reference librarian, we searched PubMed and Cochrane Database of Systematic Reviews to identify eligible SRs published after 1 October 2009 through 31 October 2014 for depression, 13 February 2015 for diabetes, and 27 February 2015 for chronic pain. Search strategies used Medical Subject Headings and free-text terms for the conditions of interest, eligible interventions, and SRs (Appendix Table 2, available at www.annals.org). We restricted the search to the past 6 years because SRs are typically outdated within 5 years of publication (28), and our goal was to describe the current state of the clinical literature. In addition to electronic searching, we screened published reviews of reviews for eligible articles.

Study Selection and Quality Assessment

Eligible SRs evaluated interventions in several broad categories (that is, medications, behavioral interventions, supervised exercise, and quality improvement or organizational interventions). We also included condition-specific interventions, such as bariatric surgery for diabetes. Reviews that evaluated mixed conditions or multiple interventions must have reported results separately for at least 1 eligible condition or intervention. We included reviews of interventions in any setting, with any type of active or inactive comparator, and with any duration of follow-up. Detailed inclusion and exclusion criteria are provided in Appendix Table 3 (available at www.annals.org).

Two investigators screened citations for eligibility, and citations that were considered to be relevant by either person were retained for full-text review. Full-text articles were reviewed by 2 investigators, and disagree-ments were resolved through discussion or adjudicated by a third person.

Formal assessment of review quality was beyond the scope of this project. However, we noted whether reviews originated from organizations known for high-quality reviews (that is, Cochrane Collaboration, Agency for Healthcare Research and Quality Evidence-based Practice Centers, and VHA ESP). For reviews reporting sex effects, we also assessed industry funding and whether statistical power was considered.

Data Abstraction

Data were abstracted by 1 investigator and reviewed by a second person. Disagreements were resolved by discussion or by a third reviewer. Abstracted data included the analysis method (that is, qualitative synthesis, meta-analysis, network meta-analysis, or individual-patient data [IPD] meta-analysis); clinical conditions; interventions; main outcomes; number and design of primary studies (for example, randomized, controlled trials [RCTs] or observational cohorts); proportion of women in the included primary studies; and if sex

effects were part of the study aims, analysis plan, or results. For reviews reporting sex effects, we also recorded the number of primary studies used for sex-specific analyses, effect estimates, and the method used (for example, metaregression, subgroup analysis, or IPD meta-analysis).

All eligible reviews on depressive disorders and chronic pain conditions were fully abstracted. All diabetes reviews of nonpharmacologic interventions were also fully abstracted. For eligible diabetes medication reviews (n = 120), we applied an additional prioritization procedure before full abstraction. We prioritized reviews that examined multiple classes of medications or evaluated a single class of medications when 6 or fewer eligible reviews were identified. For SRs evaluating a single class (>6 eligible reviews were identified), we used additional prioritization criteria (for example, the most recent review published in a high-impact journal or work done by an organization known for high-quality reviews). The remaining unselected but eligible reviews (n = 58) had a keyword text search for sex effects and were fully abstracted only when this search yielded positive results (n = 13).

Data Synthesis and Analysis of SRs

We grouped eligible reviews by intervention category and described the overall volume of clinical literature for interventions addressing each condition of interest. We also determined the number of reviews reporting sex effects and summarized these results. Time trends for the proportion of these reviews were examined for depression and diabetes.

Examination of Primary RCTs for Selected Interventions

We anticipated that some interventions for each condition would have few or no eligible SRs that addressed sex effects. Thus, for a subset of interventions for each condition, we evaluated primary RCTs to determine the feasibility of conducting a future review to evaluate sex effects. Specifically, we examined quality improvement interventions and psychotherapy for depression; diet, physical activity, and culturally tailored psychoeducation for diabetes; behavioral interventions for chronic low back pain; and exercise interventions for chronic knee osteoarthritis. We chose these intervention-condition combinations because we either could not find any review reporting sex effects or located only reviews using suboptimal methods (that is, metaregression or qualitative synthesis).

For these interventions, we identified the largest recent eligible reviews and abstracted lists of primary RCTs as candidates for examination. We then determined which of the primary trials had randomly assigned at least 75 patients per treatment group and thus might be adequately powered to evaluate the interaction between sex and treatment effects (intervention × sex) (29). We assessed whether sex effects were reported among the RCTs meeting this size requirement.

Role of the Funding Source

The VHA Quality Enhancement Research Initiative of the U.S. Department of Veterans Affairs funded this evidence map (VA-ESP Project 09–009; 2015) but had no involvement in

data collection, analysis, interpretation of the results, or the decision to submit the manuscript for publication.

Results

General Characteristics of the Evidence Base

We identified 313 eligible reviews for all conditions of interest, and we fully abstracted 268 of these (Figure 1). For both diabetes and depression, the largest SRs focused on medications; reviews on chronic pain conditions were generally smaller, with the largest SRs addressing exercise (Appendix Figure, available at www.annals.org). We also found more eligible reviews for depression and diabetes than for chronic pain conditions (Figure 1). Reviews on depression most frequently addressed psychotherapy (n = 44) and antidepressant medications (n = 24). Other interventions were evaluated by far fewer reviews (that is, combined psychotherapy and medications [n = 8], exercise [n = 7], Internet-delivered therapy [n = 4], quality improvement [n = 3], and guided self-help [n = 1]). Diabetes reviews most commonly evaluated medications (n = 120), and fewer examined exercise (n = 14); bariatric surgery (n = 12); or mixed behavioral (n = 6), dietary (n = 4), and quality improvement interventions (n = 3). Chronic pain reviews evaluated chronic low back pain (n = 26), knee osteoarthritis (n = 8), and fibromyalgia (n = 34). The most frequently evaluated interventions for chronic pain were exercise (n = 21), followed by systemic medications (n = 15), acupuncture and chiropractic manipulation (n = 12), topical medications or localized injections (n = 8), behavioral treatments (n = 8), combination interventions (n = 4), and quality improvement (n = 1).

Of 268 reviews that were fully abstracted, most were restricted to RCTs (73 for depression, 70 for diabetes, and 57 for chronic pain conditions) but only 14% (n = 37) originated from an organization known for high-quality reviews. Individual-patient data meta-analyses were also rare (n = 16 [6%]).

Sex Distribution of Included Primary Studies

Systematic reviews often did not report sex distribution of primary studies. For example, only 31% (n = 8) of reviews on chronic low back pain and 42% (n = 34) of diabetes reviews did so. However, most reviews on depression (n = 52 [60%]), knee osteoarthritis (n =5 [63%]), and fibromyalgia (n = 23 [68%]) provided data on the proportion of female participants in primary studies. When reported, women constituted the majority of participants for depression interventions; however, few of the recent large reviews evaluating either psychotherapy or combined psychotherapy and medications reported sex distributions. Diabetes reviews reported that the number of female participants varied, with studies ranging from fewer than 30% to greater than 90%. Chronic pain reviews generally included primary studies with 50% or greater female participants; in particular, fibromyalgia studies had even greater female representation (median, 96%).

Intervention Sex Effects

A small fraction of eligible SRs reported sex effects on intervention efficacy or the risk for adverse events. Sex effects were addressed by 16% (n = 14) of depression reviews (30–43),

whereas only 7% (*n* = 13) of diabetes reviews (44–56) and 8% (*n* = 2) of chronic low back pain reviews (57, 58) did so. Detailed review characteristics and sex effects are provided in Appendix Table 4 (available at www.annals.org), and summary results are presented in the Table. We found no reviews reporting sex effects for knee osteoarthritis or fibromyalgia; examination of sex effects would be very difficult for fibromyalgia, given its much higher prevalence among women than men (3.4% vs. 0.5% for U.S. adults) (59).

Depression reviews reporting sex effects most frequently addressed antidepressant medications (*n* = 6) (30–35); then psychotherapy (n = 5) (36–40); and finally combined psychotherapy and medications (*n* = 1) (41), guided self-help (*n* = 1) (42), and collaborative care (*n* = 1) (43) (Figure 2). Diabetes reviews most often evaluated sex effects for medications (*n* = 10) (44–53), and far fewer addressed bariatric surgery (*n* = 2) (54, 55) or diabetes self-management education (*n* = 1) (56) (Figure 2). The 2 chronic low back pain reviews examined sex effects for medications (57) and pain rehabilitation programs (58).

Although most reviews used metaregression to evaluate sex effects, 9 used subgroup analysis or IPD meta-analysis (4 for depression [34, 35, 42, 44] and 5 for diabetes [48, 50–53]) (Table 1). Depression reviews used IPD meta-analyses to examine the efficacy of desvenlafaxine (34), duloxetine (35), and guided self-help (42) for reducing depressive symptoms; subgroup analysis was used in a review on collaborative care, also with the main outcome of reducing symptoms (43). Diabetes reviews used subgroup analyses to examine dipeptidyl peptidase-4 inhibitors as a class (50), linagliptin (52), vildagliptin (53), and pioglitazone (48); these reviews addressed various outcomes, including glycemic control. One diabetes review applied both subgroup and IPD analyses to evaluate the efficacy of linagliptin for glycemic control (51). Both reviews reporting sex results for chronic low back pain used metaregression (57, 58) (Table). Of note, most reviews examining sex effects did not discuss any consideration of statistical power required for detecting differences between men and women. In addition, all reviews using IPD meta-analysis had industry funding or conflicts of interest noted by the authors (34, 35, 42, 51) (Appendix Table 4).

We also examined the reporting of sex effects by depression and diabetes reviews per year and found no evidence of changing trends from 2010 to 2014 (Figure 3). The proportion of eligible depression reviews reporting sex effects was 11% to 26% (mean, 17%); the percentage of diabetes reviews presenting sex effects was 5% to 11% (mean, 8%). The 2 chronic low back pain reviews reporting sex effects were published in 2013 and 2014.

To evaluate whether trends have changed since 2014, we updated PubMed searches through 13 January 2016 and found an additional 91 eligible SRs (524 abstracts screened). Seven reviews (8%) reported sex effects (3 for depression [60–62], 2 for diabetes [63, 64], and 1 each for knee osteoarthritis [65] and fibromyalgia [66]), and 47 (52%) described the sex distribution of included primary studies. Two reviews used metaregression to evaluate sex effects (60, 62), 4 used subgroup or IPD techniques (61, 63–65), and 1 applied qualitative synthesis (66) (Appendix Table 5, available at www.annals.org).

Primary RCTs: Evaluation of Sex Effects

To identify potential sex effects reported by primary RCTs, we examined trials included in the largest, most recent eligible SRs for selected interventions. For depression, we evaluated collaborative care (67) and psychotherapy (68). We found that all 21 RCTs on collaborative care had randomly assigned 75 or more participants per group, but only 2 RCTs evaluated subgroup effects by sex and found no effect on outcomes (69, 70). Only 11% of psychotherapy trials (n = 10 of 92) met the minimum sample size criterion, and 1 of these may have evaluated sex as a moderator (that is, "no demographic characteristic … moderated time to remission") (71).

For diabetes, we selected dietary (72), mixed behavioral (73), and culturally tailored psychoeducation (74) interventions. Six of 20 (30%) primary RCTs on dietary interventions (75–80) had a minimum of 75 participants per group; among these, 2 evaluated sex as a moderator and found no differential effects on glycemic control (76) or weight (78). Only 12% (n = 2 of 17) mixed behavioral RCTs (81, 82) met the sample size criterion, 1 of which reported a greater effect of physical activity on glycemic control in men than women (81). Of 33 psychoeducation RCTs, 11 met the sample size requirement (83–93) but only 1 of these evaluated sex effects and found no differences in glycemic control or diabetes knowledge (83).

We also examined exercise for knee osteoarthritis (94) and behavioral interventions for chronic low back pain (95). Seven of 30 (23%) back pain RCTs (96–102) randomly assigned at least 75 participants per group, but none evaluated sex effects. Eight of 54 (15%) knee osteoarthritis RCTs (103–110) met the sample size requirement, 1 of which stated, "both sexes … showed similar improvement in self-reported disability, pain and 6-minute walk distance" (104).

Discussion

To our knowledge, this is the first evaluation of the reporting of sex effects by SRs. Very few SRs reported sex effects, and they often failed to describe the proportion of women in primary studies. Of those reporting sex effects, most used metaregression instead of subgroup analysis or IPD meta-analysis. Metaregression is subject to ecological fallacy, potentially leading to incorrect inferences about relationships between outcomes and individual characteristics when actual associations being tested involve group characteristics; as such, metaregression is generally recommended only for study design characteristics (for example, primary vs. specialty care settings) (111, 112). In contrast, both subgroup and IPD meta-analyses are better suited to evaluate sex effects; in particular, IPD moderator analyses can directly assess whether sex interacts with intervention efficacy or the risk for adverse events (113).

To better understand the feasibility of conducting new SRs examining sex effects, we also evaluated a selection of primary RCTs for various interventions. Overall, we found that few RCTs had sufficient sample sizes to examine moderator effects. Of these, only 9 of 66 (14%) examined interactions between sex and the intervention group. The paucity of RCTs

examining sex effects is disappointing but consistent with previous work evaluating published clinical trials (114, 115).

Evaluation of sex effects by RCTs would be costly because of the larger sample sizes needed to examine moderator effects and additional resources needed to recruit an adequate number of women. Possible barriers to participation by women include fear and distrust of research, lack of transportation, and interference with work or family responsibilities (116). Meta-analyses would permit pooling of results from smaller trials, which would provide greater power to detect subgroup and moderator effects. However, metaregression, which is the technique most easily applied using published trial results, is not well-suited to examine sex effects. The IPD meta-analysis, which is the more robust approach for evaluating sex effects, could overcome small sample sizes or lower participation by women. However, obtaining patient-level data requires cooperation and sharing of data among investigators, capacity for data repositories, adequate protections for patient privacy (117), and greater statistical resources (113). Recent calls to require standardized sharing of IPD for published clinical trials (118), if heeded, could enable analyses capable of properly examining sex effects.

An intermediate step could be pooled subgroup analyses, using separate results for men and women reported by primary RCTs. These meta-analyses could employ published data and thus require fewer resources than IPD techniques. However, we identified few RCTs that reported such subgroup analyses, which may reflect concerns of the authors (and reviewers) about identifying spurious subgroup effects in underpowered studies (119, 120). Another explanation may be that subgroup analyses are being performed, but not reported, when no differences are found for men and women. Therefore, systematic and unbiased reporting of subgroup effects would be needed to support pooled analyses that accurately examined effects for women separately from men.

The following considerations may help prioritize interventions for the greater investment required for larger RCTs or IPD meta-analysis. Basic science, preclinical, or early-phase clinical studies suggest sex effects (for example, animal models and pharmacokinetics); observational studies or small RCTs indicate sex effects, but methodological limitations decrease confidence in their findings. Unique biological events (for example, menopause) or behavioral and sociocultural differences between women and men are particularly relevant for the disease process or treatment mechanism being considered.

For example, we can apply these considerations to the question of adverse effects for antidepressants. Antidepressants are used for a wide range of conditions, including depression and chronic pain. Pharmacokinetic evidence supports different antidepressant doses for men and women (121). Although data were limited and conflicting, our results also suggest that adverse effects may differ for men and women with some antidepressants. Because adverse effects are a major cause of poor adherence, a better understanding of sex effects for various antidepressants could help clinicians tailor treatment and improve outcomes.

Our study has several limitations. Evidence mapping gives a broad overview of the evidence base for important clinical and research questions and often includes multiple conditions or

interventions. Because of this increased breadth of content, however, it does not permit formal evaluation of quality (for example, for risk of bias) for included studies. Our search was also limited to reviews published since 2009, so we may have missed older reviews, especially those that studied interventions with a smaller evidence base. Reviews finding no evidence of sex effects may simply have been underpowered. All IPD meta-analysis reviews were industry-funded and used conveniently available data sets instead of systematic searches to identify all eligible trials; they are at higher risk for bias.

Despite these limitations, our results indicate that SRs and RCTs rarely examined sex effects. When reported, sex effects were generally small and analysis approaches were suboptimal. Addressing these critical gaps in the knowledge of sex effects will require adequate representation of women and study designs and data-sharing infrastructure that support sex-specific analyses. We recommend that all RCTs and SRs report the proportion of men and women enrolled and evaluate sex effects whenever appropriate.

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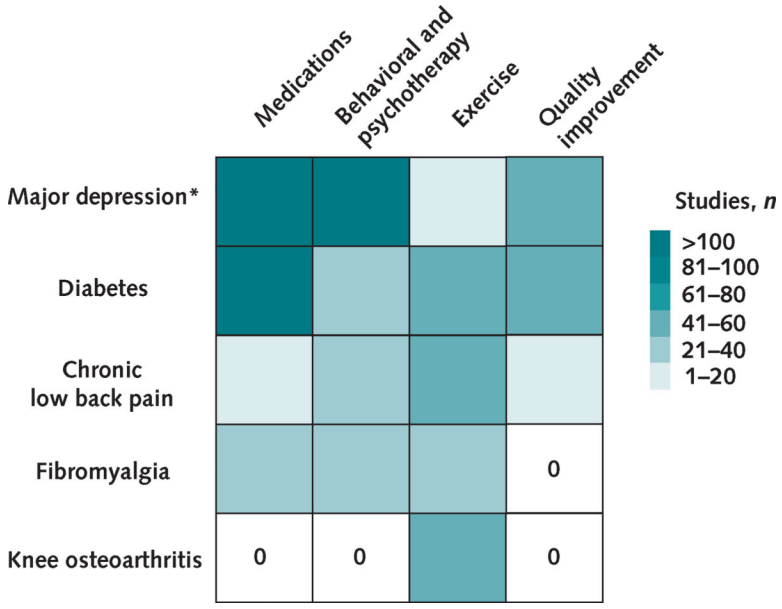
Appendix



Appendix Figure.

Primary studies included in the largest eligible SR for key interventions addressing conditions of interest.

SR = systematic review.

* Some reviews included studies with other depressive disorders.

Appendix Table 1.

Conditions Presented to Stakeholders for Prioritization*

Conditions affecting both men and women
Alzheimer disease
Anxiety (general anxiety disorder, panic disorder)
Osteoporosis
Coronary artery disease (chronic angina)
Coronary artery disease (acute coronary syndrome/myocardial infarction)
Chronic obstructive pulmonary disease Cerebrovascular disease (ischemic stroke)
Depression (major depressive disorder and dysthymia)
Diabetes mellitus, type 2 Eating disorders
Connective tissue disease (fibromyalgia)
Headache (migraine)
Hepatitis C HIV
Hyperlipidemia
Hypertension
Irritable bowel syndrome
Incontinence
Insomnia
Joint disorders (osteoarthritis: hip and knee)
Joint disorders (rheumatoid arthritis)

Obesity/overweight Chronic pain	
Post traumatic stress disorder	
Spine disorders (chronic low back pain)	
Substance use disorder Traumatic brain injury Thyroid disorders Tobacco use disorder	
Conditions specifically affecting women	
Contraceptive care Infertility	
Menstrual disorders (abnormal uterine bleeding)	
Menopausal disorders	
Depressive disorders (postpartum depression)	
Depressive disorders (premenstrual dysphoric disorder)	
Prenatal care	

* Stakeholders were allowed to assign up to 3 stars per condition and limited to 11 stars total per stakeholder.

Appendix Table 2.

Search Strategies

Set Number	Query	Results
Depressive disorders		
PubMed(searched31 October 2014)		
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]	87 024
2	Search “Psychotherapy”[Mesh] OR “BehaviorTherapy”[Mesh] OR acceptance therap*[tiab] OR commitmenttherap*[tiab] OR cognitive therap*[tiab] OR behavioral therap*[tiab] OR behaviortherap*[tiab] OR behaviourtherap*[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]	172 225
3	Search “antidepressive agents”[Pharmacological Action] OR “antidepressive agents”[MeSH Terms] OR “antidepressive”[tiab] OR antidepressant*[tiab]	141 775
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]	154 585
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]	
6	Search #1 AND (#2 OR #3 OR #4 OR #5)	32 393
7	Search #5 AND (systematic[sb] OR “Systematic Review”[tiab] OR meta-analysis[tiab] OR “meta analysis”[tiab])	1792
8	Search #6 NOT ((“Adolescent”[Mesh] OR “Child”[Mesh] OR “Adolescent”[Mesh]) NOT “Adult”[Mesh])	1677
9	Search #7 NOT (“Animals”[Mesh] NOT “Humans”[Mesh])	1677
10	Search #7 NOT (“Animals”[Mesh] NOT “Humans”[Mesh]) Filters: published in the last 5 years	631
Cochrane Database of Systematic Reviews (searched 31 October2014)		

Set Number	Query	Results
1	major depressive disorder:ti,ab,kw (Word variations have been searched)	2783
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 Yearfrom 2009 to 2014, in Cochrane Reviews (Reviews only) and Other Reviews	117
Diabetes mellitus, type 2		
PubMed(searched31 February2015)		
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]	97 698
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]	220 517
3	Search #1 AND #2	31 000
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”[<dummy_suppl>Supplementary Concept] OR “detemir”[tiab] OR “insulin degludec”[Supplementary Concept] OR “degludec”[tiab]	162 510
5	Search #1 AND #4	18 805
6	Search “Exercise”[Mesh] OR “Exercise”[tiab] OR “Exercise Therapy”[Mesh] OR “physical activity”[tiab]	296 513
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]	83 630

Set Number	Query	Results
9	Search #1 AND #8	2694
10	Search “Bariatric Surgery”[Mesh] OR “Bariatric Surgery”[tiab]	17 552
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]	554 128
13	Search #1 AND #12	3965
14	Search #3 OR #5 OR #7 OR #9 OR #11 OR #13	41 293
15	Search #14 NOT ((“Adolescent”[Mesh] OR “Child”[Mesh] OR “Infant”[Mesh]) NOT “Adult”[Mesh])	40 423
16	Search #15 NOT (“Animals”[Mesh] NOT “Humans”[Mesh])	37 107
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
Cochrane Database of Systematic Reviews (searched 13 February2015)		
1	type 2 diabetes:ti,ab,kw (Word variations have been searched)	9951
2	Type 2 Diabetes Mellitus or “Type II Diabetes Mellitus” or “Adult-Onset Diabetes Mellitus” or “Adult Onset Diabetes Mellitus” or “Maturity-Onset Diabetes Mellitus” or “Maturity Onset Diabetes Mellitus” or “Non-Insulin-Dependent Diabetes Mellitus” or “Non-Insulin Dependent Diabetes Mellitus” or “Noninsulin Dependent Diabetes Mellitus” or “Ketosis-Resistant Diabetes Mellitus” or “Ketosis Resistant Diabetes Mellitus” or “Stable Diabetes Mellitus”	6746
3	{or #1-#2} Publication Yearfrom 2009 to 2015, in Cochrane Reviews (Reviews and Protocols)	170
4	hypoglycemic agent:ti,ab,kw (Word variations have been searched)	5402
5	Metformin or “Glyburide” or “Glipizide” or “glibenclamide” or “Gliclazide” or “glimepiride” or “repaglinide” or “nateglinide” or “pioglitazone” or “rosiglitazone” or “Acarbose” or “miglitol” or “sitagliptin” or “vildagliptin” or “saxagliptin” or “Linagliptin” or “alogliptin” or “colesevelam” or “Bromocriptine” or “canagliflozin” or “dapagliflozin” or “empagliflozin” or “exenatide” or “liraglutide” or “albiglutide” or “Lixisenatide” or “dulaglutide” or “pramlintide”	7432
6	insulin:ti,ab,kw (Word variations have been searched)	24 021
7	Lispro or “Aspart” or “glulisine” or “isophane” or “glargine” or “detemir” or “degludec”	1552
8	exercise:ti,ab,kw (Word variations have been searched)	42 817
9	physical activity:ti,ab,kw (Word variations have been searched)	8033
10	Resistance Training or “Running” or “Jogging” or “Swimming” or “Walking” or “Exercise” or “Exercises” or “physical activity” or “aerobic activity” or “Sports”	61 264
11	weight reduction:ti,ab,kw (Word variations have been searched)	3204
12	weight control intervention:ti,ab,kw (Word variations have been searched)	37
13	nutrition support service:ti,ab,kw (Word variations have been searched)	5
14	nutrition support team:ti,ab,kw (Word variations have been searched)	6
15	weight loss:ti,ab,kw (Word variations have been searched)	7793
16	diet:ti,ab,kw (Word variations have been searched)	25 945
17	weight loss surgeries:ti,ab,kw (Word variations have been searched)	14
18	Bariatric Surgery	628
19	multidisciplinarytreatment plan:ti,ab,kw (Word variations have been searched)	0
20	quality improvement:ti,ab,kw (Word variations have been searched)	849
21	Patient Care Management or “multidisciplinary care” or “shared medical appointments” or “chronic disease management” or “stepped-care models” or “stepped-care model” or	2041

Set Number	Query	Results
	"stepped care models" or "stepped care model" or "nurse managed clinic" or "nurse managed clinics" or "Cell Phones" or "smartphone applications" or "Quality Improvement"	
22	{or #4-#21}	108 534
23	{and #3, #22}	134
Chronic pain conditions		
PubMed (searched 27 February 2015)		
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]	41 472
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 ("BehaviorTherapy"[Mesh] OR "psychoeducation"[tiab] OR "CBT"[tiab] OR "biofeedback"[tiab] OR (("therapy"[tiab]) AND ("mindfulness"[tiab] OR "cognitive"[tiab] OR "behavior"[tiab] OR "behavioral"[tiab] OR "relaxation"[tiab] OR "acceptance"[tiab])))	92
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-InflammatoryAgents, Non-Steroidal" [Pharmacological Action] OR "Anti-InflammatoryAgents, Non-Steroidal"[Mesh] OR "NSAIDs"[tiab] OR "Nonsteroidal Anti InflammatoryAgents"[tiab] OR "Nonsteroidal Anti InflammatoryAgent"[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

Set Number	Query	Results
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 Database of Systematic Reviews (searched 27 February2015)		
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 Yearfrom 2009 to 2015, in Cochrane Reviews (Reviews and Protocols)	88

Appendix Table 3.

Detailed Inclusion and Exclusion Criteria for Review Eligibility

Review Characteristic	Inclusion Criteria	Exclusion Criteria
Depressive disorders		
Population	Adults with major depressive disorder, persistent depressive disorder (dysthymia), subsyndromal depression, minor depression, or depression-NOS	Focus on bipolar disorder, grief, premenstrual dysphoric disorder, psychotic depression, depression subtypes (e.g., atypical depression and melancholic depression), or subsets of depressed patients who have a specific comorbid medical condition (e.g., diabetes, heart disease) or psychiatric illness (e.g., alcohol misuse)
Intervention	Antidepressants (SSRI, SNRI, TCA) Psychotherapy: CBT, CT, IPT, MBCT, PST, short-term psychodynamic therapy, reminiscence therapy delivered in person, in groups, or by internet Supervised exercise Guided self-help based on principles of CBT Quality improvement and organizational interventions: collaborative care, co-located care, women-only clinic	Alternative: dietary supplements (e.g., fish oil; vitamin D), yoga, acupuncture, St. John's wort, SAM-e Medications: atypical antipsychotics, ketamine, adjunctive medications used for augmentation (e.g., 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 (e.g., switching antidepressants) Interventions to prevent depressive disorder (e.g., interferon therapy for hepatitis C) without a specific focus on yoga
Outcome	Depressive symptoms, functional status, health-related quality of life, adverse effects	Provider outcomes, adherence or acceptance of intervention, and prevalence or cost of intervention*
Diabetes mellitus, type 2		
Population	Adults with type 2 diabetes mellitus†	None
Intervention	Oral medications: metformin, incretin mimètics (e.g., saxagliptin, exenatide and liraglutide), sulfonylureas (e.g., glipizide and glyburide), thiazolidinediones (e.g., pioglitazone) Insulin Exercise programs: aerobic or strengthening, performed in organized groups or with supportfrom health professional‡ Behavioral: psychoeducation, weight control program§ Bariatric surgery Quality improvement and organizational interventions: multidisciplinary care,	Interventions to prevent diabetes Alternative: dietary supplements, acupuncture, meditation-based interventions (e.g., transcendental meditation) Medications: medications or class of medication not listed in the included section, including insulin pump regimens, types or intensity of insulin regimens, colesevelam, alpha-glucosidase inhibitors, bromocriptine, miglitol Somatic: type or intensity of glucose monitoring Surgical interventions otherthan bariatric surgery

Review Characteristic	Inclusion Criteria	Exclusion Criteria
	shared medical appointments, chronic disease management (e.g., telephone and internet-based interventions), stepped-care models, nurse-managed clinics, women-only clinic, smartphone applications	Quality improvement and organizational interventions: endocrinology clinics, quality improvement interventions with clinician as intervention target (e.g., decision support via computer reminders)
Outcome	Glycemic control, weight, mortality, microvascular and macrovascular events[//], adverse effects[¶]	Provider outcomes, adherence or acceptance of intervention, and prevalence or cost of intervention[*]; patient blood pressure, lipids
Chronic pain conditions		
Population	Adults with musculoskeletal causes of chronic low back pain, fibromyalgia, or chronic knee pain due to osteoarthritis	Focus on only acute back or knee pain, other pain syndromes (e.g., patellofemoral)
Intervention	Antidepressants: SNRIs (duloxetine, venlafaxine, milnacipran), TCAs, SSRIs Calcium channel 2δligands (back pain and fibromyalgia): pregabalin, gabapentin Muscle relaxants (back pain and fibromyalgia) Topical treatments: NSAIDs, capsaicin, lidocaine patch Joint injection: steroid (back and knee pain), hyaluronic acid (knee pain only) 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 (e.g., physical therapist and pool therapy), as part of a class (e.g., yoga class and tai chi), or as medically directed self-care Integrative and complementary medicine (back pain and fibromyalgia): acupuncture; spinal manipulation (chiropractic care) Quality improvement and organizational interventions: multidisciplinary pain clinic, co-located care, women-only clinic; telephone-based care Self-management strategies used to decrease pain symptoms	Complementary and integrative medicine: massage, dietary supplements Medications: acetaminophen, oral NSAIDs, anti-epileptics (exceptfor gabapentin, pregabalin), antispasmodics, antipsychotics, clozapine, benzodiazepine, or opioids Marijuana/ cannabinoids Injections/physical: nerve blocks, therapeutic ultrasound, traction, back braces, knee braces, TENS unit, trigger point injections Surgical interventions (e.g., spinal fusion, total hip or knee arthroplasty, and spinal cord stimulator) Therapies: dialectical behavioral therapy, music therapy, traditional long-term psychodynamic therapy, pet therapy Treatment sequencing (e.g., acetaminophen then NSAID) Interventions to prevent chronic pain
Outcome	Pain severity, functional status	Provider outcomes, adherence or acceptance of intervention, and prevalence or cost of intervention[*]
All conditions		
Comparator	Active or inactive control	None
Timing	Any duration of follow-up	None
Setting	Any setting	None
Study design	Systematic reviews or individual-patient data meta-analyses; must have search strategy, eligibility criteria, and analysis/ synthesis plan	Reviews of single medications unless: 1) the class of medications has only 1 or 2 representative(s) available for clinical indication (e.g., metformin and pioglitazone for diabetes, and duloxetine for fibromyalgia), or 2) review is an individual-patient data meta-analysis
Publication	English language Published October2009 or later	Non-English language Published before October2009

CBT = cognitive behavioral therapy; CT = cognitive therapy; IPT = interpersonal therapy; MBCT = mindfulness-based cognitive therapy; NOS = not otherwise specified; NSAID = nonsteroidal anti-inflammatory drug; PST = problem-solving therapy; SAM-e = S-adenosylmethionine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TENS = transcutaneous electrical nerve stimulation.

[*] If reported alone, without patient health outcomes as specified in inclusion criteria,

[†] Mixed diabetes populations were included if patients with type 2 diabetes were analyzed separately.

[‡] Includes tai chi, PiIates, yoga, and related forms of exercise.

[§] Includes supervised programs that use changes in physical activity, diet, or a combination of these approaches to achieve weight change or improved glycemic control.

[//] Includes stroke, cardiac event (e.g., myocardial infarction), nephropathy, neuropathy (including diabetic foot ulcer), and changes in cognition.

[¶] Includes cancer, osteoporosis, hypoglycemia, changes in cognition, lactic acidosis, adverse gastrointestinal effects, and serious adverse events.

Appendix Table 4.

Characteristics and Results for Systematic Reviews Reporting Sex Effects

Author, Year (Reference)	Studies, n	RCTs, n	Female,	% Intervention	Main Outcomes	Analysis Method	Sex Effect Estimate	Industry Funding or COI?	Considered Statistical Power?
Depressive disorders									
Calati, 2013(30)	34	34	NR	3 classes of antidepressants (SSRIs, SNRIs, and TCAs)	Depressive symptoms	Metaregression	"…[M]ale gender had a negative influence on efficacy of ant ¡depressant treatment" (slope estimate −1.336, P <0.0001, for 4 weeks and −2.268, P <0.0001 for 6 week outcomes; nonsignificant estimates for 2 and 8 weeks)	No	No
Carter, 2012 (31)	76	NR	NR	Antidepressants, various	Depressive symptoms, remission	Qualitative synthesis	1) 2 RCTs, sertraline vs. imipramine: "Women taking sertraline showed significantly greater response and remission rates than those taking imipramine; no difference between treatments for men." "Women tended to respond better to sertraline and men to imipramine." 2) 1 RCT, duloxetine vs. placebo: "Female gender was consistently associated with poorer response and remission…" 3) 1 meta-analysis of RCTs, venlafaxine or SSRI vs. placebo: "treatment response was found to be independent of gender."	Yes (sponsored by EliLilly, manufacturer of fluoxetine and duloxetine)	No
Gartlehner, 2011 (32)	234	118	NR	2nd generation antidepressants, various classes	Depressive symptoms, adverse effects (sexual dysfunction)	Qualitative synthesis	"Efficacy trials usually did not address differences in efficacy or effectiveness between men and women. Two head-to-head RCTs provided limited evidence on adverse sexual effects; 1 reported a higher risk for sexual dysfunction in men… receiving paroxetine…and the other reported greater sexual dysfunction in women…"	No	No
Gibiino, 2014 (33)	116	116	NR	Venlafaxine, sertraline	Depressive symptoms	Metaregression	"Female gender seems to be related to a better clinical outcome during venlafaxine treatment… whilst for sertraline a definite gender specificity was not found…" Venlafaxine 6 week outcomes: percent male slope estimate −1.43, $P = 0.007$ Sertraline 6 week outcomes: nonsignificant	Yes (speaking or consultant fees from multiple companies)	Unclear
Soares, 2014(34)	6	6	63	Desvenlafaxine	Depressive symptoms	IPD meta-analysis	"Sex, baseline [depression] score, and baseline [disability] score each significantly predicted some levels of success with…treatment but not others." (no further details reported)	Yes (funded by Pfizer, manufacturer of desvenlafaxine)	No
Mancini, 2012 (35)	6	6	66	Duloxetine	Functional remission (Sheehan disability scale)	IPD meta-analysis	"Additional significant variables were time since the first episode…and sex." (greater improvement for female vs. male: −0.99, 95% CI −1.91 to −0.07) "[T]reatment-by-variable interactions were not statistically significant…"	Yes (funded by Eli Lilly, manufacturer of duloxetine)	Unclear
Braun, 2013(36)	53	53	71	Psychotherapy, various types	Depressive symptoms	Metaregression	CBT vs. other therapies, more effective with greater proportion of female patients (slope estimate −0.009, 95% CI −0.0156 to −0.0029)	No	Unclear
Driessen, 2010 (37)	132	132	NR	Psychotherapy (mostly CBT)	Depressive symptoms	Metaregression	Nonsignificant slope for percentage of women	No	No
Driessen, 2010 (38)	23	11	NR	Short-term psychodynamic	Depressive symptoms	Meta regression	"[T]he percentage of women did not predict treatment effects…"(nonsignificant slopes for multiple outcomes)	No	No
Cuijpers, 2012 (39)	52	52	NR	Antidepressants vs. psychotherapy	Depressive symptoms	Qualitative synthesis	"[M]edication was significantly more effective than psychotherapy in patients with…postnatal depression, and depressed infertile women. However, the results…were each based on only one study." Postnatal depression: Hedges' g −0.48 (95% CI −0.75 to −0.22) Infertile women: Hedges' g −0.94 (95% CI −1.47 to −0.41)	No	Yes
Roshanaei-Moghaddam, 2011 (40)	21	21	NR	CBT vs. antidepressants, various classes	Depressive symptoms	Metaregression	"[P]otential confounds explored in sensitivity analyses included: demographics (average age, percent Caucasian, percent female), medication type…[T]he strongest association was for year of study…No other potential confounds…were significantly related to effect size."	No	No

Author, Year (Reference)	Studies, n	RCTs, n	Female,	% Intervention	Main Outcomes	Analysis Method	Sex Effect Estimate	Industry Funding or COI?	Considered Statistical Power?
von Wolff, 2012 (41)	8	8	55–81	Combined psychotherapy and antidepressants vs. antidepressants alone	Depressive symptoms	Meta regression	"[S]ample characteristics of the studies such as mean age, percentage of women…were not associated statistically significantly with differences in effect sizes…"	No	Yes
Bower, 2013(42)	16	16	"generally 2/3 to 3/4 were women	Guided self-help	Depressive symptoms	IPD meta-analysis	"There was no evidence that this main [intervention] effect varied by age, sex, intervention type, or study quality."	Yes (author employed by GAIA AG, Germany, owns one of included interventions)	Yes
Thota, 2012 (43)	32	NR	NR	Collaborative care	Depressive outcomes	Subgroup analysis	"Significant differences were found between different categories…[for] the following variables: organization, case manager, and collaborative care components." (stratified analyses performed for majority female vs. majority male and estimates given, but sex was not in list of significant differences)	No	No
Diabetes mellitus, type 2									
Esposito, 2012 (44)	218	218	NR	8 classes of medications, including insulin and oral drugs	Proportion achieving goal HbA_{1c} <7.0%	Meta regression	"…[P]otential sources [of heterogeneity] were explored with a meta-regression analysis including…gender (% of male, <50% vs. ≥50%), mean age…[These analyses] failed to disclose a significant role for any of these factors…"	No	No
Kramer, 2013 (45)	7	2	NR	Short-term intensive insulin	Insulin resistance	Metaregression	"In univariate meta-regression models, sex was the only covariate associated with the heterogeneity between studies (P <0.0001)…The decrement in [insulin resistance] induced by intensive insulin therapy increased as the proportion of men deceased."	No	No
Lapane, 2013 (46)	21	9	33–75	Sulfonyl ureas	Risk of falls and fractures	Qualitative synthesis	1) 1 RCT used subgroup analysis to compare fracture risk for glyburide vs. rosiglitazone, showed RR 0.37 (95% CI 0.23–0.61) for women and RR 0.85 (95% CI 0.52–1.40) for men 2) 1 RCT used subgroup analysis to compare sulfonylurea vs. rosiglitazone (both in addition to metformin) for fracture risk, showed RR 0.53 (95% CI 0.38–0.73) for women and RR 0.69 (95% CI 0.0.46–1.03) for men 3) 2 cohort studies "showed a trend of elevated risk of fractures associated with [sulfonylureas] among men but not among women."	No	No
Lamanna, 2011 (47)	35	35	21–100	Metformin	CV events (12 RCTs); CV mortality (10 RCTs); all-cause mortality (5 RCTs)	Metaregression	"At meta-regression, [metformin] appeared to have a more beneficial effect on all-cause mortality in trials…enrolling a higher proportion of women (Intercept: 2.237 [0.184–4.290); Slope: −0.039 [−0.076 to −0.003], P = 0.034)."	Yes (consultancy and speaking fees, and research grants from multiple companies)	Yes
He, 2014(48)	10	1	NR	Pioglitazone	Risk for bladder cancer	Subgroup analysis	"Three studies were identified for subgroup analysis stratified by gender…reveal[ing] a conspicuous association between pioglitazone and bladder cancer for men (HR 1.64; 95% CI 1.01–2.67) but not for women (HR 1.69; 95% CI 0.64–4.47)."	No	Yes
Fakhoury, 2010 (49)	38	38	33–57	Incretin mimetics	Glycemic control, weight, adverse events (hypoglycemia)	Metaregression	"… [A]nalyses were conducted controlling for heterogeneity by adjusting for key study covariates (age, study duration,…gender…)" and covariates with significant effects noted in results; gender not listed as such for any outcome	Unclear (no COI statement, authors employed by for-profit IMS Health, UK)	No
Esposito, 2011 (50)	43	43	NR	DPP-4 inhibitors	Glycemic control, weight, adverse events (hypoglycemia)	Metaregression and subgroup analysis	"Gender, mean age, concomitant oral drug use and trial duration…did not significantly influence the response in the meta-regression analysis, or subgroup analysis for [glycemic control]."	No	No
Groop, 2014 (51)	3	3	49–56	Linagliptin	Glycemic control	Subgroup analysis and IPD meta-analysis	Women: MD −0.72, 95% CI −0.89 to −0.56 Men: MD −0.58, 95% CI −0.75 to −0.41 $P = 0.25$ for interaction with treatment group	Yes (funded by Boehringer Ingelheim, manufacturer of linagliptin)	No
Johansen, 2012 (52)	8	8	45	Linagliptin	Composite of fatal and nonfatal major CV events, and hospitalization for unstable angina	Subgroup analysis	Women: HR 0.96, 95% CI 0.21–4.37 Men: HR 0.25, 95% CI 0.10–0.60	Yes (funded by Boehringer Ingelheim,	No

Author, Year (Reference)	Studies, n	RCTs, n	Female,	% Intervention	Main Outcomes	Analysis Method	Sex Effect Estimate	Industry Funding or COI?	Considered Statistical Power?
								manufacturer of linagliptin)	
Schweizer, 2010 (53)	25	25	44–45	Vildagliptin	Composite of various CV events and CV death	Subgroup analysis	Women: RR 0.78, 95% CI 0.44 to 1.38 Men: RR 0.87, 95% CI 0.60 to 1.24	Yes (funded by Novartis, manufacturer of vildagliptin)	No
Wang, 2015 (54)	15	0	NR	Bariatric surgery	Diabetes remission	Metaregression	"[M]eta-analysis results showed an insignificant association between gender and [diabetes] remission."	No	No
Parikh, 2013 (55)	39	3	0–91	Bariatric surgery	Glycemic control, diabetes remission	Metaregression	"Among the baseline characteristics, age, BMI, sex, and mean HbA1c were not significant predictors of remission."	No	No
Gucciardi, 2013 (56)	13	10	69–100	Diabetes self-management education	Glycemic control	Qualitative synthesis	From 10 studies, 18 intervention features were associated with positive effects	No	NA
Chronic low back pain									
Cawston, 2013 (57)	15	15	45–63	Duloxetine	Pain severity	Metaregression	"Sources of heterogeneity were explored through meta-regression analysis…[and] only pain duration was found to be associated with treatment effect."	Yes (funded by Eli Lilly, manufacturer of duloxetine)	No
Waterschoot, 2014 (58)	18	18	32–100	Pain rehabilitation program	Disability, work participation, and quality of life	Metaregression	1) "Type of intervention, evaluation moment, and percentage of women significantly contributed to the regression equation [for disability]." (but slope estimate 0.002, P = 0.086) 2) Only "number of disciplines significantly contributed to the regression equation [for work participation]." 3) "[O]nly type of intervention contributed significantly to the regression equation [for quality of life]."	No	Yes

BMI = body mass index; CBT = cognitive behavioral therapy; COI = conflict of interest; CV = cardiovascular; DPP-4 = dipeptidyl peptidase 4; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; IPD = individual-patient data; MD = mean difference; NA = not applicable; NR = not reported; RCT = randomized, controlled trial; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Appendix Table 5.

Characteristics and Results for Systematic Reviews Reporting Sex Effects From Search Update*

Author, Year (Reference)	Studies, *n*	RCTs, *n*	Female, %	Intervention	Main Outcomes	Analysis Method	Sex Effect Estimate	Industry Funding or COI?	Considered Statistical Power?
Depressive disorders									
Biesheuvel-Leliefeld, 2015(60)	25	25	70	Psychotherapy	Depressive symptoms, relapse/recurrence	Meta regression	Proportion women was used in metaregression and "not associated with the effect size."	No	No
Cuijpers, 2014 (61)	14	14	68	CBT, antidepressants	Depressive symptoms, relapse/recurrence	IPD meta-analysis	"None of the analyses showed that gender significantly moderated outcome of CBT versus pharmacotherapy… We also found no evidence that gender was a nonspecific predictor of outcome within modality…"	No	Yes
Sim, 2015(62)	45	NR	60–70	Antidepressants and/or psychotherapy	Depressive symptoms, relapse	Metaregression	Proportion of women was not significantly associated with efficacy in the intermediate or long-term for antidepressants, or long-term for psychotherapy.	No	No
Diabetes mellitus, type 2									
Thrasher, 2015 (63)	8	8	53	Linagliptin	relapse Mean change in HbA_{1c} at 18 and 24 weeks	IPD meta-analysis	"[L]inagliptin efficacy is maintained irrespective of baseline HbA_{1c}, BMI, duration of diabetes, age, or sex."	Yes (funded by Boehringer Ingelheim, manufacturer of linagliptin)	No
Blonde, 2015(64)	4	4	50	Canagliflozin	Achieving goal HbA_{1c}<7.0%, or >5% weight loss	IPD subgroup analysis	1) OR for HbA1c <7.0%: Women: 2.6 (95% CI 1.8–3.6) for 100 mg and 5.1 (3.6–7.4) for 300 mg Men: 4.1 (2.8–6.0) for 100 mg and 8.5 (5.8–12.6) for 300 mg 2) OR for weight loss:Women: 4.7 (2.8–7.8) for 100 mg and 6.2 (3.7–10.3) for 300 mg Men: 5.2 (3.1–8.8) for 100 mg and 8.3 (5.0–13.8) for 300 mg	Yes (funded by Janssen, manufacturer of canagliflozin)	No
Knee osteoarthritis									
Strand, 2015(65)	29	29	22–100	Intra-articular hyaluronic acid	Pain and function	Subgroup	RCTs with 67% or more women: SMD 0.54 (95% Cl 0.30–0.77) for pain, 0.63 (0.36–0.89) for function; RCTs with <67% women: SMD 0.32 (0.14–0.49) for pain, 0.25 (0.1 0–0.39) for function; $P = 0.01$ for difference between subgroups in function: "Studies with higher proportions of female patients yielded better knee function outcomes."	Yes (funded by HA Viscosupplement Coalition, multiple companies)	No
Fibromyalgia									
Forte, 2015 (66)	34	22	89–100	Duloxetine	Pain	Qualitative synthesis	"[F]our RCTs that assessed duloxetine effects by sex offered insufficient evidence of a mixed pattern; in three there was no difference by sex at 3 and 6 months, but in one study, females improved more than males at 3 months ($P = 0.046$)."	No	NA

BMI = body mass index; CBT = cognitive behavioral therapy; COI = conflict of interest; CV = cardiovascular; DPP-4 = dipeptidyl peptidase 4; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; IPD = individual-patient data; MD = mean difference; NA = not applicable; NR = not reported; RCT = randomized, controlled trial; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

BMI = body mass index; CBT = cognitive behavioral therapy; COI = conflict of interest; HbA_{1c} = hemoglobin A_{1c}; IPD = individual-patient data; NA = not applicable; NR = not reported; OR = odds ratio; RCT = randomized, controlled trial; SMD = standardized mean difference.

*Updated searches of PubMed were performed on 13 January 201 6, using same search strategies described in Appendix Table 2. Overall, 524 citations were screened, leading to 91 eligible reviews (1 8 for depression, 44 for diabetes, and 29 for chronic pain). In addition to results shown here, targeted data abstractions for all eligible reviews included method of synthesis and reporting on sex distribution of primary studies.

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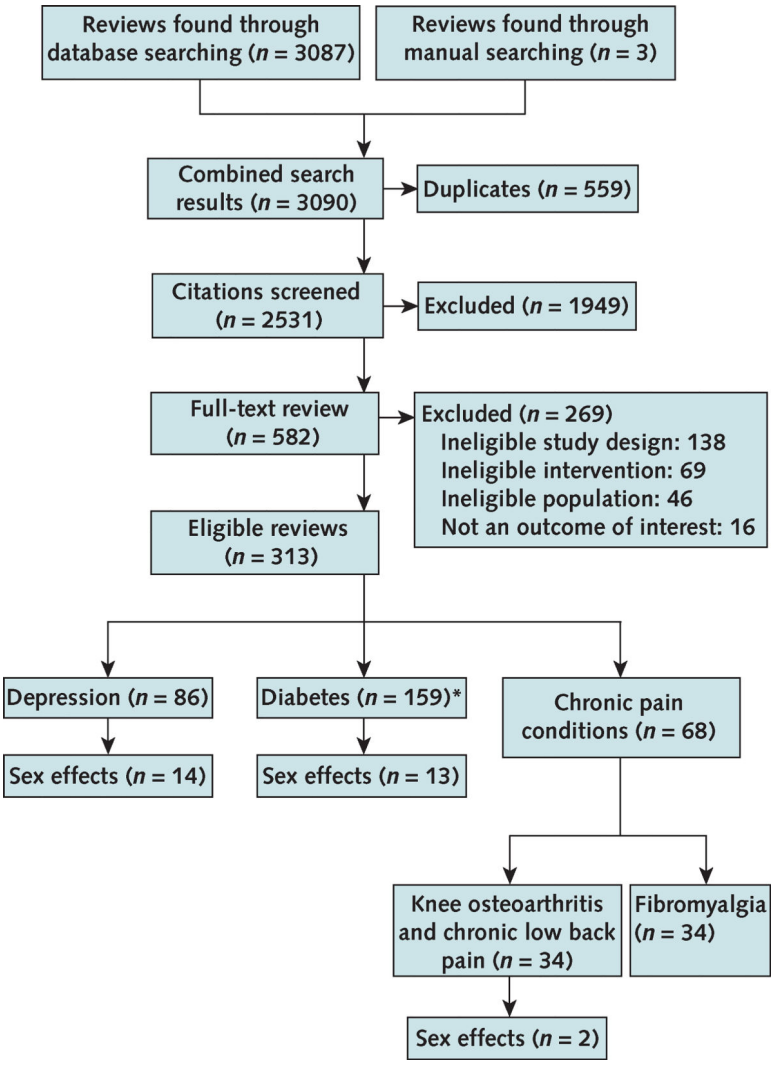

Figure 1.

Summary of evidence search and selection.

* 114 of 159 eligible diabetes reviews were fully abstracted. The remaining 45 reviews received a keyword text search and were not further abstracted because of negative search results.

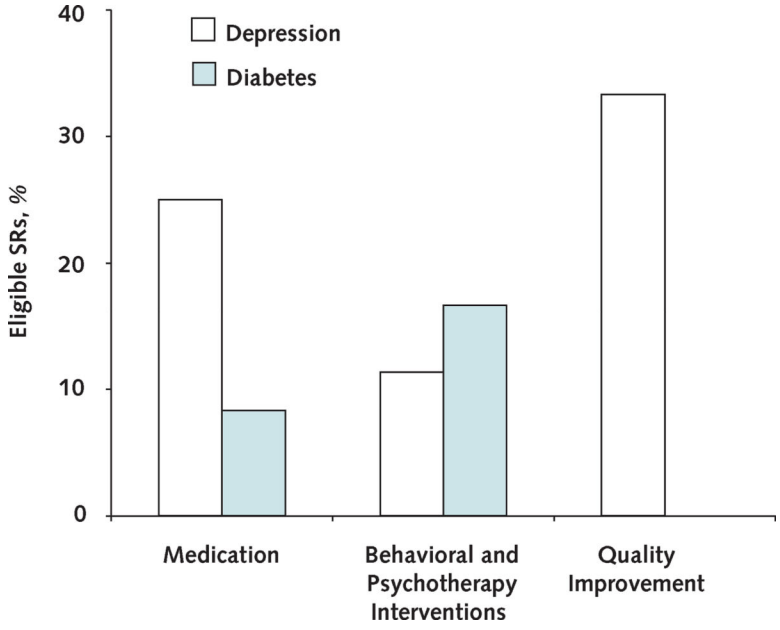

Figure 2.

Proportion of eligible SRs reporting sex effects for depression and diabetes.

In addition, 2 diabetes reviews reported sex effects for bariatric surgery; 1 depression review examined sex effects for combined medications and psychotherapy; 1 depression review reported on guided self-help; and 2 reviews on chronic low back pain looked at sex effects for medications and pain rehabilitation programs, respectively. No reviews on knee osteoarthritis or fibromyalgia reported sex effects. SR = systematic review.

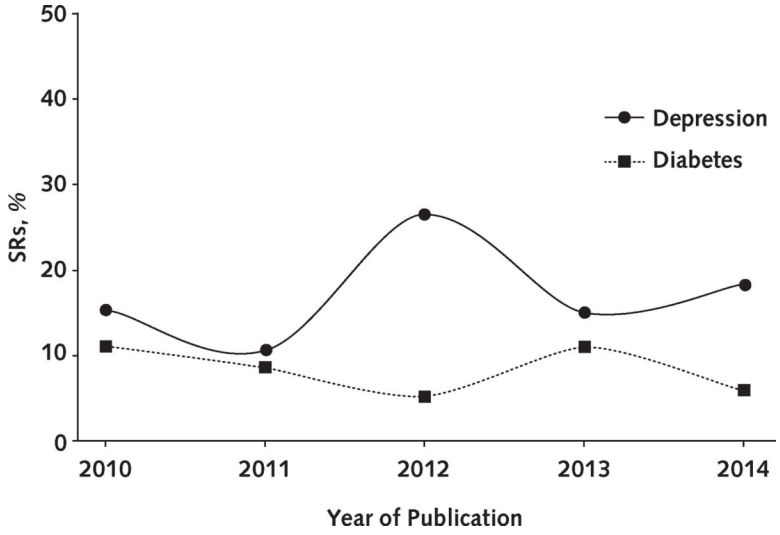

Figure 3.

Proportion of eligible SRs reporting sex effects for depression and diabetes from 2010 to 2014.

SR = systematic review.

Table.

Summary of Reported Sex Effects for Major Outcomes in Depression, Diabetes, and Chronic Low Back Pain*

Outcome, by Condition	Intervention	Reviews Reporting Sex Effects, *n*			
		Possible Differences		Possibly No Differences	
		Metaregression	IPD or Subgroup	Metaregression	IPD or Subgroup
Depression					
Improved symptoms or function	Antidepressants	2	1	-	-
	Psychotherapy†	1	-	3	-
	Other‡	-	-	-	2
Diabetes					
Glycemic control	Medications§	-	-	2	2
	Bariatric surgery	-	-	1	-
Weight loss	Incretin mimetics	-	-	1	-
	Bariatric surgery	-	-	1	-
Cardiovascular events or mortality	Medications§	1	1	-	1
Adverse effects	Medications§	-	-	1	1
Chronic low back pain					
Improved pain or function	Duloxetine	-	-	1	-
	Rehabilitation program	1	-	-	-

IPD = individual-patient data.

*Appendix Table 4 (available at www.annals.org) shows detailed information on systematic review characteristics, study populations, and sex effects. In addition to quantitative results summarized here, 4 systematic reviews reported qualitative syntheses about sex effects: 3 on medications for depression (2 on depressive symptoms and 1 on adverse effects) and 1 on diabetes (on adverse effects associated with medications).

†Various types, both alone or combined with other interventions.

‡One review on guided self-help and 1 review on collaborative care.

§Many types. See Appendix Table 4 for more information.