QUERI

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

September 2015

Prepared for:

Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

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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.

Recommended citation: Duan-Porter W, Goldstein K, McDuffie J, Clowse M, Hughes J, Klap R, Masilamani V, Allen LaPointe NM, Williams JW Jr. Mapping the Evidence: Sex Effects in High-impact Conditions for Women Veterans. VA ESP Project #09-010; 2015.

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%).

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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