Inclusion of Women and Gender-Specific Analyses in Randomized Clinical Trials of Treatments for Depression

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Abstract

Background: The higher prevalence and cost of depression for women compared with men and the possible gender differences in treatment response demand the inclusion of women in clinical trials of depression treatments. The 1993 National Institutes of Health (NIH) Revitalization Act set a new standard, requiring investigators to consider the inclusion of women and analyze outcomes by gender, yet compliance with these standards in depression research has not been examined systematically. The purpose of this study is to examine the inclusion of women and gender-specific analyses in recent randomized clinical trials (RCTs) for depression.

Methods: RCTs were identified through a MEDLINE search for trials published between January 1 and December 31, 2007, and a Clinicaltrials.gov search of self-identified interventional studies to treat depression.

Results: Of the 150 RCTs for depression published in 2007, 15% did not report the gender composition of their sample, 50% of studies did not analyze outcomes by gender, and 12% controlled for gender but did not analyze for gender differences. Of the 768 trials reviewed on Clinicaltrials.gov, 89% reported recruiting male and female participants, yet <1% reported an intention to analyze results by gender.

Conclusions: Many recent studies of depression treatments include women but do not examine outcomes by gender. Understanding how women differ from men in response to treatment is critical for enhancing treatment efficacy for the greatest number of adults with depression.

Introduction

THE HISTORICAL EXCLUSION OF WOMEN from many clinical research studies has led to concerns about women's access to safe, appropriate clinical treatment.¹ In 1985, the National Institutes of Health (NIH) established a Public Health Service Task Force on Women's Health,² and their recommendations of increased attention to women's health issues led NIH to develop specific guidelines in 1986 regarding the inclusion of women as subjects in NIH-funded extramural research.³ This policy encouraged both the inclusion of women in clinical research and the evaluation of gender differences in health outcomes. The United States General Accountability Office (GAO, formerly the General Accounting Office) reported in 1990 that the policy had not been adequately communicated or implemented within the NIH or the broader research community.⁴ Subsequently, a Clinical Equity Provision was included in the 1993 NIH Revitalization Act (Public Law 103-43),⁵ making it a requirement that women be considered for inclusion in all NIH-funded human subject research. The aim of the Clinical Equity Provision

within the 1993 NIH Revitalization Act was to ensure that the efficacy of treatments for women are scientifically determined and not extrapolated from data derived from male participants, as had been done previously. The act states that trials be "designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women . . . differently than other subjects in the trial."⁵ Thus, the act requires both the participation of women and the ability to conduct gender-specific analyses on outcomes.

At the same time that the 1993 NIH Revitalization Act went into effect, the Food and Drug Administration (FDA) reexamined their 1977 guidelines, which had excluded "women of childbearing potential" from participating in early studies of drugs (i.e., phase I and early phase II studies).⁶ There were significant concerns that this restrictive policy had resulted in a lack of information about how women would respond to medications tested exclusively on men, lack of information about the effects of female physiology (e.g., menstrual cycle, oral contraceptives) on drug actions, and a general lack of participation by women in drug development studies.

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Although the new guidelines did not mandate inclusion of women in medication studies or gender-specific analyses of outcomes, the FDA lifted their restriction, allowing women to participate in medication development studies and stated their support of the inclusion of women in research.

A number of literature reviews over the past 15 years find that, despite these early efforts, women continued to be underrepresented in clinical trials, and few studies conducted gender-specific analyses. Vidaver et al.⁷ examined all federally funded clinical research studies published in four major journals during the years 1993, 1995, 1997, and 1998. In each year, approximately one fifth of published studies excluded female participants, and the majority of studies enrolling both men and women did not examine results by gender (67%–75%). A review of articles published in the *New England Journal of Medicine* during a similar time period (1994–1999)⁸ found that 86% of the 120 trials that were examined did not conduct gender-specific analyses, and studies supported by “government/NIH funding” were not more likely than studies funded by other sources to analyze results by gender. These findings are consistent with the GAO’s 2000 report⁹ that found that the enrollment of women in research had increased since 1993; however, less progress had been made in terms of increasing the level of analyses by gender. The GAO recommended continued efforts to improve the representation of women in all aspects of research, including the analysis and reporting of findings. The GAO further recommended that a data system be established to store and disseminate information about NIH-funded research on women’s health issues. This recommendation was to develop into the current Clinicaltrials.gov online registration system for clinical trials (described further below).

Recent reviews suggest that despite continued recommendations, researchers have not increased their attention toward gender-specific analyses. Geller et al.¹⁰ examined 46 federally funded U.S. clinical trials published in nine major journals in 2004 and found that 87% of studies did not report outcomes by gender or include gender as a covariate in analyses. In their review of 239 phase I and II clinical trials published in three major journals in the year 2001, Fleisch et al.¹¹ found that two thirds of these medication trials excluded women and 90% of studies did not conduct gender-specific analyses, suggesting that the FDA’s guidelines had not been followed. Further, 91% of studies of drugs that had previously shown gender differences in pharmacokinetics or adverse drug reactions did not analyze outcomes by gender. A similar lack of attention to gender-specific analyses of outcomes has been reported in reviews of cardiovascular disease (CVD),¹² smoking cessation,¹³ and nursing¹⁴ research.

Why is it important to include women in research on treatments for depression?

The 1993 NIH Revitalization Act defined “women’s health conditions” as those that are “unique to, more serious, or more prevalent in women.”⁵ Depression is one of the most common psychological disorders in the United States, with a lifetime prevalence of 16.2% and a 12-month prevalence of 6.6%.¹⁵ Consequences of depression include extensive personal and societal costs related to health, psychological functioning, and work productivity.^{16–21} Women are more likely than men to suffer from depression,^{22,23} a gender difference that occurs

across the life span.²⁴ Women are also more likely than men to report so-called atypical symptoms of depression (e.g., hypersomnia), comorbid anxiety disorders, and to attempt suicide.¹⁶

According to the NIH Revitalization Act, “women’s health conditions” are further defined as conditions “for which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women.”⁵ Men and women may differ in their response to medications for several reasons, including differences in pharmacokinetics, pharmacodynamics, menstrual cycle effects, and effects of gender-specific coadministration with oral contraceptives.^{11,16,25–27} Mixed results have been found for gender differences in response to depression pharmacotherapies (see Gorman¹⁶ for review). For example, a review of 30 studies of tricyclic antidepressants (TCAs)²⁸ concluded that there were no overall gender differences in response yet found more favorable outcomes for women in some studies and more favorable outcomes for men in other studies. Research on selective serotonin reuptake inhibitors (SSRIs) has shown similarly mixed results. Whereas some studies of SSRIs found no gender difference in response (e.g., Thiels et al.,²⁹ Hildebrandt et al.³⁰), other studies have reported differences, including a recent large-scale study by Young and et al.³¹ that reported a better response to the SSRI citalopram by women. Evidence has also suggested gender differences in response to behavioral treatments for depression.³² In sum, it is currently unclear whether men and women differ in their response to medical and behavioral interventions for depression.

Because of the high rates and costs of depression for women and questions about differences in response to treatment by gender, it is critical that women are represented in research on treatments for depression and that gender differences are examined to ensure that all persons with depression have access to the most efficacious treatments available.

Aims of the current review

The Clinical Equity Provision in the 1993 NIH Revitalization Act was written to ensure that women receive sufficient representation in treatment research, especially for disorders in which the prevalence or treatment may differ for women and men, such as depression. It is clear that gender-specific analyses are not conducted in the majority of published studies in general, but the extent to which women are represented in depression treatment research has not yet been systematically examined. The purpose of this study is to address this gap in the literature by reviewing the inclusion of female participants and gender-specific analysis in recent clinical trial research on depression. Two systematic reviews were conducted of (1) all clinical trials for depression published during the year 2007 and (2) all interventional studies for depression listed on Clinicaltrials.gov. It was expected that a minority of these studies would report gender-specific analyses.

Materials and Methods

Study design

We conducted a MEDLINE search of clinical trials for depression published between January 1, 2007, and

December 31, 2007, using the search terms “randomized clinical trial” and “depression.” After removal of duplicate articles and articles that were not studies of diagnosed major depression, the remaining articles were individually examined to determine if they met inclusion criteria; namely, they were randomized clinical trials (RCTs) for depression and published in English. Information on the journal of publication, sample size, and type of funding was collected for each article that met the criteria for inclusion. Data on the number and percent of female participants included in each sample were collected and, each article was classified (yes/no) as to whether it included (1) gender composition of the sample, (2) gender as a variable in the analyses, (3) gender as a covariate in the analyses, and (4) *a priori* gender-specific hypotheses as part of the analysis plan.

To further examine the inclusion of gender in RCTs of depression using the most current data available, a second search was conducted on Clinicaltrials.gov. The Clinicaltrials.gov website (www.Clinicaltrials.gov) is a registry of over 68,000 clinical trials conducted in the United States and around the world. U.S. Public Law 110-85 (FDA Amendments Act of 2007 [FDAAA]), Title VIII, Section 801, mandates that clinical trials of drugs, biologics, and devices be registered at Clinicaltrials.gov. Clinicaltrials.gov was accessed from March 20 to March 24, 2009. Records on Clinicaltrials.gov were individually examined for gender composition and information about analyzing results or controlling analyses by gender, including stratifying by gender.

Statistical analysis

In addition to frequency and descriptive statistics, chi-square and Fisher's exact tests were used to determine if the report of gender composition or inclusion of gender in analyses differed by funding source or sample size. Statistical analyses were performed using SPSS v.16.0 software for PC (SPSS, Inc.). Statistical tests were two-tailed and differences were considered significant when $p < 0.05$.

Results

Results of MEDLINE review

Of 222 original articles published during 2007, 72 studies were excluded for the following reasons: 53 were not RCTs, 13 were trials of a condition other than depression, and 6 were not published in English. The 150 RCTs included in the review were published in 95 different journals. Sample sizes ranged from 9 to 4041, with a mean of 292 participants (standard deviation [SD] = 503). Studies examined pharmacological treatments (38%), behavioral treatments (24%), or a combination of pharmacological and behavioral treatments (30%), with 8% examining “other” treatments (e.g., electroconvulsive therapy). Thirty percent of the studies reported receiving funding from the NIH, 55% reported funding from other sources (e.g., pharmaceutical companies), and 15% did not list the source of funding.

Fifteen percent of the 150 studies ($n = 22$, Fig. 1) did not report the gender composition of the samples; 10 studies excluded male participants, and 2 studies excluded female participants. For 11 of 12 studies, the intervention was directed toward a subgroup within one gender (e.g., pregnant women, men with prostate cancer) or a rationale was provided for the inclusion of just one gender (e.g., the higher rates of depression and lack of treatment options for childbearing women). One article examining depression in women who had undergone coronary artery bypass surgery did not provide a rationale for excluding men.

Of the RCTs that reported enrolling both men and women ($n = 116$), women composed between 2% and 87% of the sample (mean = 55.5%, median = 59%). Fifty percent of the studies did not analyze their results by gender, and 88% did not include *a priori* hypotheses about outcomes by gender. Sixteen percent of studies controlled for gender in analyses and did not analyze for gender differences. Studies funded by the NIH were not more likely than studies funded through other sources to report gender-specific analyses (chi-square = 0.19, $df = 1$, $p = 0.66$).

FIG. 1. Percent of studies reviewed based on a MEDLINE search of clinical trials for depression published during the year 2007 that did not report gender composition, did not include gender as a variable in the analyses, did not control for gender in the analyses, and did not include gender as a variable in the hypotheses. The percent for Gender Composition Not Reported is based on a total of 150 studies reviewed on MEDLINE. Percents for all other variables are based on 116 studies that reported including both male and female participants.

Because a small sample size might not provide sufficient statistical power to conduct analyses by a subgroup, such as gender, the sample sizes of studies that did and did not conduct gender-specific analyses were examined. A large range of sample sizes was found both for studies that did (range 19–4041) and studies that did not (range 9–2876) conduct gender-specific analyses. The average sample size of the studies that reported gender-specific analyses (mean = 348, SD = 200) did not differ from studies that did not report gender-specific analyses (mean = 256, SD = 399; $t = 1.09$, $df = 146$, $p = 0.28$).

Results of ClinicalTrials.gov review

Seven hundred sixty-eight interventional studies of depression (including phases I, II, III, and IV studies) were listed on ClinicalTrials.gov at the time of database access (Fig. 2). One study did not complete the requirement to specify whether they were recruiting men and women, men only, or women only. Eighty-nine percent of the 767 studies were recruiting both male and female participants, and the remaining 10.7% ($n = 82$) specified recruiting only male ($n = 10$) or female ($n = 72$) participants to study a subgroup of adults within that gender (e.g., men with erectile dysfunction, gay men, pregnant women, postmenopausal women). Of the studies that included both male and female participants ($n = 685$), only 5 studies (<1%) referenced gender as part of their study design, analysis plan, or hypotheses. Two studies planned to control for gender in their analyses (1 by stratifying by gender), and 3 studies planned to analyze results by gender. An additional 5 studies reported that they would either control for or analyze by “demographic variables” without specifying gender. Of the 10 studies that mentioned gender or demographic variables, 6 were funded through the NIH, 1 was funded through another source within the United States, and 1 was funded by a source outside of the United States.

FIG. 2. Percent of studies reviewed based on a ClinicalTrials.gov search of self-identified interventional studies of depression that did not report gender composition and did not report including gender as part of the study design or analysis plan. The percent for Gender composition not reported is based on a total of 768 studies reviewed on ClinicalTrials.gov. The percent for Gender not reported to be part of the study design or analysis plan is based on 685 studies that reported including both male and female participants.

Discussion

NIH requires that women be considered as participants in clinical research and that studies should provide for analysis of data by gender. Although our review demonstrates that the majority of RCTs for depression include women, as is consistent with the NIH requirement, 15% of published studies of depression did not report the gender composition of the samples. Our review further showed that the majority of publicly registered clinical trials do not appear to plan to analyze treatment outcomes by gender. In addition, NIH-funded researchers were not more likely than researchers funded by other sources to conduct gender-specific analyses. This finding is consistent with reviews of other clinical trial research (e.g., Vidaver et al.,⁷ Ramasubbu et al.,⁸ Geller et al.¹⁰). Sixteen percent of published studies covaried for gender, suggesting that although these researchers recognized potential differences in outcome by gender, they controlled for such differences rather than conducting analyses to determine (1) if there were a significant difference in health outcome for women compared with men and (2) the magnitude and direction of possible differences. These analyses are essential to clarify previously discrepant results regarding gender differences in depression treatment.

As noted in the Introduction, studies of gender differences in response to TCAs and SSRIs have shown mixed results.¹⁶ Gender differences in the pharmacokinetics of SSRIs have been reported.^{25,33} Although there is less research on gender differences in the pharmacokinetics of TCAs, TCAs are metabolized by the cytochrome P450 (CYP) isoenzyme system, which has shown gender differences,²⁵ suggesting that the pharmacokinetics of TCAs would be different for at least a subset of women compared with men. Both the potential gender differences in the pharmacokinetics of SSRIs and TCAs and the conflicting results found by prior research suggest the importance of examining gender differences in response to both of these classes of antidepressant medication in every clinical trial. However, we found that only 40% of clinical trials using a TCA medication and 49% of clinical trials using an SSRI medication that were published during the year 2007 analyzed outcome data by gender. Whereas it is important to examine gender differences in outcomes of clinical trials in general, it is crucial to conduct these analyses when there are known gender differences in the pharmacokinetics of a specific medication or conflicting results have been found in previous studies.

Because we reviewed articles from just one publication year (2007) and studies currently listed on ClinicalTrials.gov, we were not able to determine if inclusion of gender-specific analyses has increased since the 1993 NIH Revitalization Act went into effect. However, the rate of gender-specific analysis was extremely low in both reviews, suggesting that major increases have not occurred over time. In addition, other reviews have found no increase in reporting results by gender in comparisons of articles published before and after the 1993 NIH Revitalization Act (e.g., Dickerson et al.¹³). Future reviews will provide information about whether and what types of changes occur over time in terms of gender-specific analyses within depression research. A number of studies included in the review may not have had the statistical power to conduct gender-specific analyses because of small sample sizes (e.g., 10% of the studies included 30 or fewer partici-

pants), but analysis of our data suggested that there were no significant differences in the average sample size of studies that did vs. did not conduct such analyses. It is further possible that some researchers published gender-specific analyses of their trials during a year other than 2007 as part of secondary or pooled analyses. Although pooled analyses are useful to attain statistical power, the purpose of the 1993 NIH Revitalization Act was to encourage researchers to include gender-specific analyses as a primary consideration. With the evidence that men and women differ in their response to some treatments for depression, analyzing outcomes by gender in every publication, especially the primary results of a clinical trial, provides important information for both researchers and clinical treatment providers.

The 1993 Revitalization Act required NIH to create a system to store and track research on women's health, and the GAO's 2000 report cites the development of Clinicaltrials.gov as a potential source for this information.⁹ At this time, Clinicaltrial.gov does not specifically require researchers to post information about their intention to analyze outcomes by gender; however, in accordance with the FDAAA, Clinicaltrials.gov does require researchers to post summaries of their studies, including hypotheses, planned primary and secondary analyses, and the gender composition of the sample. Currently, <1% of treatment studies of depression mentioned gender as any aspect of the analysis plan, suggesting that gender is not considered to be a significant variable. There is a need for all persons and agencies involved in clinical research to work together to ensure compliance with the Clinical Equity Provision of the 1993 NIH Revitalization Act and to further our knowledge about gender differences in treatment response for depression and other disorders. On an individual level, clinical trial researchers can play a critical role by designing their studies to assess gender differences and by analyzing outcomes by gender. Journal editors can encourage compliance by including questions about gender on the forms that peer reviewers are required to complete as part of the review process and by providing feedback about the gender composition and inclusion (or noninclusion) of gender-specific analyses to the authors of every submission.

On an agency level, NIH can continue developing initiatives to elicit compliance from their funded researchers. Although NIH guidelines to grant reviewers state that "scientifically acceptable" phase III clinical trials are those that include the analysis of outcomes by gender in their recruitment and analytical plan (unless there is clear research showing no gender differences or there is a strong reason to include just one gender), the current review suggests that greater attention to and enforcement of these guidelines are needed within the grant review process. NIH can also expand their monitoring of researchers by requiring information about both gender enrollment and analyses in progress reports and grant renewal applications. Further, NIH can work with researchers to identify barriers to including women, such as concerns about increased cost or the assumption that treatments do not differ between genders, unless there is a specific identified biological reason to expect differences.¹ Clinicaltrials.gov can help to provide a comprehensive database of clinical trials by requiring researchers to publish information on gender composition, gender-specific hypotheses, and analyses when they register, update their clinical trial records, and report their results. Clinicaltrials.gov can

also develop search engines that allow researchers and government entities to more easily identify and review studies related to women's health. NIH could further monitor information related to gender analyses through RePORTER, a new online tool that provides public access to report, data, and analyses of NIH-funded research activities. At this time, the FDA is no longer excluding women from early clinical trial research yet does not require the inclusion of women or gender-specific analyses in studies. Because the current evidence suggests a continued underrepresentation of women in drug development research, the FDA may need to review their policy and consider regulations in order to provide women with equal access to research knowledge.

Conclusions

Consistent with reviews of a number of other health conditions, recent studies of treatment for depression include female participants but rarely examine outcomes by gender. Evidence suggests that men and women differ in prevalence and presentation of depression and may differ in their response to treatments. Understanding how and when women differ from men in response to depression treatment is critical for enhancing efficacy for the greatest number of adults with depression.³⁴ As government agencies, researchers, and journal editors increase their attention to gender differences in depression treatment outcomes, a better understanding of treatment interventions will result in new and targeted treatments for depression.

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Disclosure Statement

The authors have no conflicts of interest to report.

References

1. Mastroianni AC, Faden R, Federman D. Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. *Women and health research: Ethical and legal issues of including women in clinical studies*. Washington, DC: National Academy Press, 1994:Vol.1.
2. United States Public Health Service. Report of the Public Health Service Task Force on Women's Health issues. *Public Health Rep* 1985;100:73-106.
3. National Institutes of Health. NIH guide for grants and contracts. Bethesda, MD: National Institutes of Health, 1986.
4. General Accounting Office. Problems in implementing policy on women in study populations. Washington DC: United States Government Accounting Office. Report No. GAO/T-HRD-90-50, 1990.
5. Federal Register. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. 1994:59.
6. Food and Drug—Administration. Guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs. *U.S. Federal Register* 1993;58:39406-39416.

7. Vidaver RM, LaFleur B, Tong C, Bradshaw R, Marts SA. Women subjects in NIH-funded clinical research literature: Lack of progress in both representation and analysis by sex. *J Womens Health Gend Based Med* 2000;9:495–504.
8. Ramasubbu K, Gurm H, Litaker D. Gender bias in clinical trials: Do double standards still apply? *J Womens Health Gend Based Med* 2001;10:757–764.
9. General Accounting Office. Women's health: NIH has increased its efforts to include women in research. Washington, DC: United States General Accounting Office, 2000.
10. Geller SE, Goldstein Adams M, Carnes M. Adherence to federal guidelines for reporting of sex and race/ethnicity in clinical trials. *J Womens Health* 2006;15:1123–1131.
11. Fleisch J, Fleisch MC, Thurmann PA. Women in early-phase clinical drug trials: Have things changed over the past 20 years? *Clin Pharmacol Ther* 2005;78:445–452.
12. Blauwet LA, Hayes SN, McManus D, Redberg RF, Walsh MN. Low rate of sex-specific result reporting in cardiovascular trials. *Mayo Clinic Proc* 2007;82:166–170.
13. Dickerson DL, Leeman RF, Mazure CM, O'Malley SS. The inclusion of women and minorities in smoking cessation clinical trials: A systematic review. *Am J Addict* 2009;18: 21–28.
14. Crane PB, Letvak S, Lewallen L, Hu J, Jones E. Inclusion of women in nursing research (1995–2001). *Nurs Res* 2004;53: 237–242.
15. Kessler RC, Berglund P, Demler O, et al. National Comorbidity Survey Replication. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289:3095–3105.
16. Gorman JM. Gender differences in depression and response to psychotropic medication. *Gen Med* 2006;3:93–109.
17. Klerman GL, Weissman MM. The course, morbidity, and costs of depression. *Arch Gen Psychiatry* 1992;49:831–834.
18. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA* 1990;252:2524–2528.
19. Wang PS, Simon GE, Kessler RC. Making the business case for enhanced depression care: The National Institute of Mental Health-Harvard work outcomes research and cost-effectiveness study. *J Occup Environ Med* 2008;50:468–475.
20. Luppia M, Heinrich S, Angermeyer MC, König HH, Riedel-Heller SG. Cost-of-illness studies of depression: A systematic review. *J Affect Disord* 2007;98:29–43.
21. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: How did it change between 1990 and 2000? *J Clin Psychiatry* 2003;64: 1465–1475.
22. Kessler RC, McGonagle KA, Zhae S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8–19.
23. Grant BF, Hasin DS, Chou P, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States. *Arch Gen Psychiatry* 2004;61:1107–1115.
24. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 1993;29:85–96.
25. Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? *Clin Pharmacokinet* 2002;41:329–342.
26. Yonkers KA, Kando JC, Cole JO, Blumenthal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *Am J Psychiatry* 1992;149:587–595.
27. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry* 2000;157: 1445–1452.
28. Wohlfarth T, Storosum JG, Elferink AJ, van Zwieten BJ, Fouwels A, van den Brink W. Response to tricyclic antidepressants: Independent of gender? *Am J Psychiatry* 2004; 161:370–372.
29. Thiels C, Linden M, Grieger F, Leonard J. Gender differences in routine treatment of depressed outpatients with the selective serotonin reuptake inhibitor sertraline. *Int Clin Psychopharmacol* 2007;20:1–7.
30. Hildebrandt MG, Steyerberg EW, Stage KB, Passchier J, Kragh-Soerensen P, Danish University Antidepressant Group. Are gender differences important for the clinical effects of antidepressants? *Am J Psychiatry* 2003;160:1643–1650.
31. Young EA, Kornstein SG, Marcus SM, et al. Sex differences in response to citalopram: a STAR*D report. *J Psychiatr Res* 2009;43:503–511.
32. Thase ME, Reynolds CF, Frank E, et al. Do depressed men and women respond similarly to cognitive behavior therapy? *Am J Psychiatry* 1994;151:500–505.
33. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997;32(Suppl 1):1–21.
34. Mazure CM, Keita GP, eds. Understanding depression in women: Applying empirical research to practice and policy. Washington, DC: American Psychological Association, 2006.

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