Sex Differences in Depressive Response During Monoamine Depletions in Remitted Depressive Subjects

Francisco A. Moreno, M.D.; Cynthia A. McGahuey, B.A.; Marlene P. Freeman, M.D.; and Pedro L. Delgado, M.D.

Objective: Although sex differences in the prevalence of depression are well known, the effects of sex on the underlying mechanisms of illness and on antidepressant action remain less clear. Tryptophan depletion and catecholamine depletion (via α-methylparatyrosine [AMPT] administration) are broadly utilized methods for studying the effects of the safe and transient reduction of serotonin and catecholamine neurotransmission, respectively. The present study assessed the effects of sex on the mood response during acute monoamine depletion.

Method: Data on Hamilton Rating Scale for Depression (HAM-D) scores during depletion tests were analyzed retrospectively in 59 subjects (41 women, 18 men) who underwent tryptophan depletion and 39 subjects (25 women, 14 men) who underwent catecholamine depletion. All subjects were in remission from a DSM-IV–defined major depressive episode. Data reviewed included subjects enrolled between November 1993 and November 1997.

Results: Significant increases in HAM-D scores were observed in response to both depletion procedures, with a similar magnitude of change. Analysis of variance with repeated measures of HAM-D scores revealed a significant main effect of time for tryptophan depletion ($F = 7.31$, $df = 3$, $p < .01$) and for catecholamine depletion ($F = 9.61$, $df = 4$, $p < .01$). Time-by-sex interaction was significant for tryptophan depletion ($F = 4.04$, $df = 3$, $p = .01$), but not for catecholamine depletion ($F = 0.75$, $df = 4$, $p = .57$). Depressive symptoms were significantly greater in women during tryptophan depletion (t test $p < .01$), while no significant sex differences were found during catecholamine depletion.

Conclusions: These findings suggest that the effect of sex in depressive vulnerability may be related to differential sex effects in monoaminergic function.

(J Clin Psychiatry 2006;67:1618–1623)

Received June 6, 2005; accepted April 13, 2006. From the Department of Psychiatry, College of Medicine, University of Arizona Health Sciences Center, Tucson (Drs. Moreno and Freeman and Ms. McGahuey); and the Department of Psychiatry, University of Texas Health Sciences Center, San Antonio (Dr. Delgado).

Supported by the University of Arizona College of Medicine Dean's Physician Scientist Career Development Award (Dr. Moreno) and National Institute of Mental Health grant R01 MH48977 (Dr. Delgado).

Presented at the 29th annual meeting of the Society for Neuroscience, New Research Abstract 855.16, November 1999, Miami Beach, Fla.; and the 37th and 38th annual meetings of the American College of Neuropsychopharmacology, December 1998, Las Croabas, Puerto Rico, and December 1999, Acapulco, Mexico.

Financial disclosure is listed at the end of this article.

The authors thank the Arizona Hispanic Center of Excellence for logistics support; Candace Fogel, R.N., for assistance with data management; and Jeri Lizabeth Fickelman, Ph.D., for editorial contribution.

Corresponding author and reprints: Francisco A. Moreno, M.D., Department of Psychiatry, College of Medicine, University of Arizona Health Sciences Center, 1501 N. Campbell Ave., Suite 7303, Tucson, AZ 85724 (e-mail: fmoreno@e-mail.arizona.edu).

Although sex differences in the prevalence of depression are well established, the effects of sex on symptom profile, underlying mechanisms of illness, and antidepressant response require further study. Consistently across epidemiologic surveys, women are reported as suffering from major depression 2 to 3 times more commonly than men.[1–4] This difference is reportedly unrelated to ethnicity, education, income, or marital status. The natural course, quality, and severity of depressive symptoms have been inconsistently reported to vary between sexes, and this issue has led to continued debate.[5–8]

Although treatment studies reporting the effects of sex have been sparse, an intriguing trend is suggested among studies addressing these differences. Women (especially if premenopausal) may respond less favorably to imipramine and more favorably to the more serotonergic agents paroxetine, sertraline, fluoxetine, and phenelzine, while the opposite may be true for men.[9–12] Although these findings are not consistently replicated,[13] they are further supported by a finding that older women of menopausal age may have a lower rate of response to monoamine oxidase inhibitor (MAOI) and selective serotonin reuptake inhibitor (SSRI) antidepressants.[13,14] Based in a recent analysis of a large pooled dataset, Thase and colleagues[15] reported an apparently lower remission rate in older women than

in younger women. Interestingly, the findings suggested greater remission rates with the serotonin and norepinephrine reuptake inhibitor venlafaxine than with various SSRIs, and the largest difference in response rate (23% contrast) was observed in the group of older women not receiving hormone replacement therapy. This reported difference may be mediated by a decrease in serotonin-mediated antidepressant responsiveness, with a proportionally larger norepinephrine-mediated response. Thus, it is important to ascertain whether sex differences in monoamine system activity explain the sex differences observed in the prevalence of depression, its underlying pathophysiology, and treatment response differences.

Compelling data that pertain to underlying mechanisms of antidepressant action and vulnerability to depressive illness come from studies utilizing neurotransmitter depletion paradigms. Tryptophan depletion and catecholamine depletion via α-methylparatyrosine (AMPT) administration are methods commonly used to study the effects of transient and safe reduction of serotonin (5-HT) and catecholamine neurotransmission, respectively. The appeal of these paradigms results from their safety and selectivity and from the robustness of the clinical responses observed as a result of transiently induced monoamine activity changes. In healthy subjects, acute tryptophan depletion decreases the rate of brain 5-HT synthesis.[16] Nishizawa et al.[16] reported that not only were baseline rates of 5-HT synthesis significantly lower in females than in males, but the depletion effects on 5-HT synthesis were also significantly greater in females. Ellenbogen et al.[17] suggested that healthy women might be more prone to experience depressive symptoms during tryptophan depletion than men. Booij et al.[18] reanalyzed pooled data from various published studies and found that remitted depressive women were also more likely than men to experience depressive changes during tryptophan depletion, and moreover that women experienced greater depletion of plasma tryptophan than men after the administration of the same tryptophan-depletion protocol.

To our knowledge, there are no studies that address sex differences during catecholamine depletion. The present study assessed the effects of sex on the mood response to acute 5-HT and catecholamine depletion in subjects from different age groups who were in clinical remission from major depressive disorder.

METHOD

Subjects

Ninety-eight subjects who underwent neurotransmitter depletion paradigms at the Arizona Health Sciences Center were studied. Data reviewed included subjects enrolled between November 1993 and November 1997. Fifty-nine subjects (41 women, 18 men) received tryptophan depletion, and a separate group of 39 subjects (25 women, 14 men) received catecholamine depletion (AMPT). Subjects were selected from a pool of 142 potential subjects who participated in a variety of neurotransmitter depletion studies approved by the University of Arizona Human Subjects Committee and from whom written informed consent had been obtained. Subjects were selected if they had at least 1 prior episode of major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV]),[19] based on the Structured Clinical Interview for DSM-IV.[20] Subjects with residual depressive symptoms were selected if their total testing-day baseline score on the 25-item Hamilton Rating Scale for Depression (HAM-D)[21] was ≤ 15. Subjects who tested repeatedly, or did so under nonstandardized conditions (i.e., tryptophan depletion supplemented with buspirone), were excluded from this assessment. All subjects were free of general medical or neurologic conditions on the basis of the clinical history and review of systems, physical examination, electrocardiogram, routine blood tests, pregnancy test, and urine drug testing during screening. In women, the phase of menstrual cycle, proximity to menopause, and use of hormonal agents were not reliably recorded and were excluded from analysis.

Procedure

Although data regarding subjects were drawn from a variety of neurotransmitter depletion studies, each subject was administered the same tryptophan depletion or AMPT procedure during participation.

Testing was performed in the outpatient offices of the Psychopharmacology Research Program of the Department of Psychiatry at the University of Arizona Health Sciences Center. The majority of subjects were involved in a treatment protocol and continued to take antidepressant medication throughout testing, although a small portion of subjects had been in remission and medication-free for longer than 3 months. For each depletion testing day, subjects arrived at approximately 8:30 a.m., and they were allowed to move about freely, use the bathroom, and have access to drinking water or fruit juice during the test sessions. Subjects undergoing tryptophan depletion fasted overnight prior to testing and did not eat until after 4:00 p.m. Subjects read or listened to the radio at will, but did not sleep, watch television, or engage in extensive interactions.

The tryptophan depletion protocol included 2 days; on the first day, subjects were assessed prior to and after consumption of a tryptophan depletion beverage, and the second day included follow-up assessments. Behavioral ratings were obtained in the morning 15 minutes prior to (9 a.m.), 5 hours after (2 p.m.), 7 hours after (4 p.m.), and approximately 26 hours after ingestion of the amino acid drink (11 a.m. the next day). Tryptophan depletion was accomplished by ingestion of a 102-g, tryptophan free, 15–amino acid beverage as described in prior studies.[22,23]

Table 1. Demographic and Clinical Characteristics

Characteristic	Tryptophan Depletion			Catecholamine Depletion (AMPT)		
	Male	Female	All	Male	Female	All
Baseline HAM-D score, mean ± SD	5.5 ± 4.5	4.9 ± 3.7	5.1 ± 3.9	5.4 ± 3.3	4.5 ± 3.8	4.8 ± 3.6
Age when depleted, mean ± SD, y	48.1 ± 11.9	43.5 ± 12.2	44.8 ± 12.2	45.2 ± 14.4	43.1 ± 13.9	43.9 ± 13.9
Total subjects, N (%)	18 (30.5)	41 (69.5)	59 (100)	14 (35.9)	25 (64.1)	39 (100)
Treatment at time of depletion test, N (%)						
SSRI treated	10 (55.6)	19 (46.3)	29 (49.2)	5 (35.7)	10 (40.0)	15 (38.5)
Non-SSRI treated	4 (22.2)	14 (34.1)	18 (30.5)	7 (50.0)	10 (40.0)	17 (43.6)
Medication free	4 (22.2)	8 (19.5)	12 (20.3)	2 (14.3)	5 (20.0)	7 (17.9)
Age group at time of depletion test, N (%)						
< 25 y	0 (0)	2 (4.9)	2 (3.4)	2 (14.3)	2 (8.0)	4 (10.3)
25–34 y	2 (11.1)	9 (22.0)	11 (18.6)	1 (7.1)	6 (24.0)	7 (17.9)
35–44 y	5 (27.8)	11 (26.8)	16 (27.1)	4 (28.6)	5 (20.0)	9 (23.1)
45–54 y	8 (44.4)	11 (26.8)	19 (32.2)	3 (21.4)	7 (28.0)	10 (25.6)
55–64 y	1 (5.6)	6 (14.6)	7 (11.9)	3 (21.4)	3 (12.0)	6 (15.4)
> 64 y	2 (11.1)	2 (4.9)	4 (6.8)	1 (7.1)	2 (8.0)	3 (7.7)

Abbreviations: AMPT = α-methylparatyrosine, HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

Methionine, cysteine, and arginine were encapsulated because of their distinctly unpleasant taste.[24] Subjects ingested the capsules 15 minutes before drinking the remaining amino acids suspended in water (300 mL) and flavored with 30 cm^3 of chocolate syrup.

The catecholamine depletion test included 2 days of AMPT administration (1 g t.i.d. on day 1, 1 g at 9 a.m., and 1 g at 2 p.m. on day 2) and a follow-up day. Behavioral and side effect ratings were obtained twice daily (9 a.m. and 3 p.m.) during AMPT administration and on the morning of the follow-up day. Many of the subjects received diphenhydramine as an active control for AMPT at a different testing date, but a number of them did not receive it.

Given that many of the subjects did not receive adequate control testing, data on mood during the control condition are not included.

Measures for Protection of Subjects

Given the possible induction of transient depressive symptoms, the following procedures were implemented for the protection of subjects. Patients deemed at risk for suicide or other complications were excluded. Patients were advised that they would be required to stay in the hospital until assessed, debriefed, and considered safe to go home by one of the investigators. Subjects were closely monitored and carefully educated about symptomatic relapse and potential complications, were transported home by a family member or research staff, and were strongly encouraged to contact the on-call research clinician as needed. All subjects who participated were discharged without complications.

Measurements

Depression ratings at each time point were obtained with the 25-item HAM-D. Side effects from the depletion procedures were recorded with the Symptom Checklist, as described by Woods et al.[25] Ratings were performed by experienced research-clinicians with established reliability (κ scores ≥ .85). Repeated ratings on each patient were performed by the same clinician whenever possible. In studies that included the use of control tests, subjects and raters remained blinded to the sequence of testing.

Data Analysis

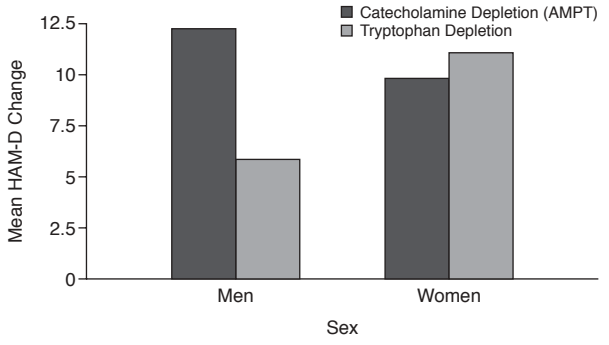
Change in depressive scores (HAM-D) was assessed by analysis of variance (ANOVA) in a repeated-measures design. This allowed for an assessment of the main effect of time and gender-by-time interaction. The Tukey test was used to assess the significant interactions revealed by ANOVA. Raw scores were analyzed with a t test. A "categorical relapse" during testing was defined as a ≥ 100% increase of HAM-D score with a minimum total score of 18. Spearman correlation was used to assess the relationship between sex and change in HAM-D score, as well as sex and categorical relapse during testing. Categories of age groups were also created in order to assess the interaction of age and sex combined. Categories are intended to represent standard age categories and may not reflect the subject's reproductive life-phase. The groups were as follows: group 1 = ≤ 24 years, group 2 = 25 to 34 years, group 3 = 35 to 44 years, group 4 = 45 to 54 years, group 5 = 55 to 64 years, group 6 = ≥ 65 years.

Results were considered significant when $p \leq .05$. Trends are also reported when $p \leq .10$. All tests were 2-tailed. Bonferroni correction is proposed for the ANOVA of time and the tests for interaction of sex, age, and age group in both tryptophan depletion and AMPT datasets. The corrected p value considered significant for the ANOVA results is ≤ .0125. Data analysis and graphic presentation utilized the SPSS computer program.[26]

RESULTS

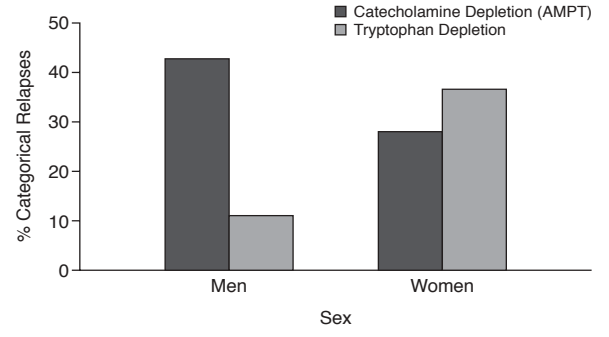
Sample characteristics are shown in Table 1. Subjects experienced depressive responses during both monoamine depletions. Repeated-measures ANOVA of HAM-D scores

Figure 1. Sex Differences in HAM-D Change During Monoamine Depletions



Abbreviations: AMPT = α-methylparatyrosine, HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Sex Differences in Categorical Depressive Response During Monoamine Depletions



Abbreviation: AMPT = α-methylparatyrosine.

revealed a significant main effect of time of similar magnitude for tryptophan depletion ($F = 7.31$, $df = 3$, $p < .01$) and for catecholamine depletion ($F = 9.61$, $df = 4$, $p < .01$). Time-by-sex interaction was significant for tryptophan depletion ($F = 4.04$, $df = 3$, $p = .01$), but not for catecholamine depletion ($F = 0.75$, $df = 4$, $p = .57$). Women experienced greater depressive responses than men during tryptophan depletion (mean ± SD HAM-D score change = 11.10 ± 8.35 for women vs. 5.89 ± 6.63 for men, $p = .02$), but not during catecholamine depletion (9.84 ± 7.33 for women vs. 12.29 ± 7.69 for men) (Figure 1). Spearman correlations of sex and change in HAM-D score and of sex and categorical relapse were statistically significant during tryptophan depletion ($r = –0.31$, $p = .02$, and $r = –0.26$, $p < .05$, respectively), but not during catecholamine depletion ($r = 0.15$, $p = .35$, and $r = 0.15$, $p = .36$, respectively). Both for the group as a whole and for each sex, there was no significant effect of chronological age or age group during either depletion.

Similar findings were observed when categorical depressive responses were considered. During catecholamine depletion, 13/39 subjects (33.3%) experienced relapse (6/14 men [42.9%] and 7/25 women [28.0%]). During tryptophan depletion, 17/59 subjects (28.8%) experienced relapse (most notably, only 2/18 men [11.1%], but 15/41 women [36.6%]) (Figure 2). Post hoc analysis of the effects of specific antidepressant and of antidepressant group received at the time of depletion testing showed no significant interaction with main effect of time for either tryptophan or catecholamine depletion. Similarly, when Symptom Checklist score was used as a measure of adverse events and tolerability during testing, there were no interactions of time by gender by Symptom Checklist scores.

All participants returned to their baseline mood after testing. None of these subjects required additional clinical care for symptoms induced by or complications from neurotransmitter depletions.

DISCUSSION

Although similar depressive symptoms were observed during tryptophan and catecholamine depletions, men showed depressive responses during tryptophan depletion that were significantly less than in women, and no sex differences were observed during catecholamine depletion with AMPT. The marked difference in vulnerability to depressive responses during tryptophan depletion is consistent with results from previous studies indicating that healthy women have lower baseline 5-HT synthesis rates and experience a greater degree of decrease in plasma tryptophan and in 5-HT synthesis during tryptophan depletion.[16,18] Similarly, healthy and recovered depressive women experience greater depressive changes than men during tryptophan depletion,[17,18] but it is intriguing that the same sex difference is not observed during catecholamine depletion with AMPT. We may speculate that the sexual dimorphism associated with the effects of gonadal hormones during development and other factors influencing clinical expression may be modified by a series of compensatory and modulatory mechanisms that preferentially affect a specific neurotransmitter system. It is possible that serotonin-related pathways might be drastically influenced by sex hormones while catecholamine-mediated circuits remain unaffected.

A number of uncontrolled factors may influence the response to tryptophan depletion, including the dose of amino acid drink, which was uniform regardless of body weight and perhaps led to greater plasma depletion of tryptophan in smaller subjects. The levels of tryptophan and large neutral amino acids are not available for analysis. The phase of menstrual cycle and use of gonadal hormones were not prospectively recorded. We reiterate that data in this study were drawn from a variety of depletion

studies, and differences in length of time in remission, use of different antidepressants, and varied doses and durations resulted in a greater heterogeneity of the sample. In addition, since control preparations had been used in only a portion of the subjects, the study is unable to rule out placebo effects during depletions. These and other issues may limit the interpretation of the results, due to their potential influence on the mood response to monoamine depletions.

Despite the caution dictated by the above limitations of this retrospective analysis, the findings are robust and congruent with the background literature presented. The lack of sex effects observed during catecholamine depletion (in contrast to the tryptophan depletion findings) suggests that although men may be less vulnerable to 5-HT–mediated expression of depressive symptoms, such resilience is not observed when the catecholaminergic system is challenged.

Studies support that biological differences may underlie different vulnerabilities between males and females. In 5-HT_{1B} knockout mice, female animals had a larger stress-model vulnerability in the forced swim test and the tail suspension test during 5-HT depletion.[27] Depressive symptoms during tryptophan and catecholamine depletion in humans are associated with similar changes in activity in prefrontal and limbic structures.[28,29] However, sex differences in regional cerebral glucose utilizations have been reported in the posterior cingulate cortex of remitted depressive human subjects during tryptophan depletion, although not in other regions of interest.[30]

It is generally accepted that gonadal hormones are responsible for the majority of brain structural and functional differences between the sexes. These include variations in size of nuclei, number of neurons contained in these nuclei, and patterns of branching and circuitry connections.[31] Besides these organizational or permanent effects, gonadal hormones affect programming of these circuits, allowing for temporary regulation.[32]

In addition, monoamine neurotransmitter receptors interact closely with reproductive hormones. In a study done in rodents, ovariectomy prevented the decrease in 5-HT_2 binding sites induced by the serotonin and norepinephrine reuptake inhibitor imipramine in the cerebral cortex but failed to prevent the same changes in β-adrenergic receptors.[33] This finding was reversed by administration of estradiol, progesterone, or a combination of both. Since down-regulation of 5-HT_2 and β-adrenergic receptors is generally accepted as a central marker of antidepressant response, the specificity of the Kendall et al.[33] findings suggests that ovarian hormones play a permissive role in serotonergic activity that is perhaps crucial for 5-HT_2 down-regulation, a dynamic not observed for the β-adrenergic receptor. It has been postulated that the complex fluctuations in levels of gonadal hormones, estrogen in particular, throughout the female reproductive lifespan facilitate vulnerabilities to depressive symptoms premenstrually, postpartum, and during perimenopause.[14,34] These findings are consistent with the notion that 5-HT function may be influenced by sex. An improved understanding of the biological functions underlying sex differences in affective disorders may help inform treatment interventions.

Further studies are needed to determine whether these differences relate to the neurotransmitter depletion test itself, or if they reflect true sex differences between the catecholaminergic and serotonergic pathways involved in the regulation of mood states. Future depletion studies should prospectively control for variables hypothesized to affect outcome such as magnitude of depletion and tolerability concerns; include a careful assessment of the impact of reproductive hormones, phase of menstrual cycle, and menopausal status; and consider a within-subject sequential depletion design.

Drug names: buspirone (BuSpar and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Financial disclosure: Dr. Moreno has received grant/research support from the National Institute of Mental Health and Cyberonics, has been a consultant for Cyberonics and Forest, and has been a speaker for Cyberonics, Forest, and Wyeth-Ayerst. Dr. Freeman has been a consultant for Ther-Rx and Reliant Pharmaceutical; has received grant/research support from the National Institute of Mental Health, the U.S. Food and Drug Administration, Forest, and Pronova; has received honoraria from Pfizer, Eli Lilly, and AstraZeneca; and has been on the speakers/advisory board of AstraZeneca. Dr. Delgado has received grant/research support from the National Institute of Mental Health, AstraZeneca, Eli Lilly, GlaxoSmithKline, Organon, Forest, and Corcept and honoraria from Wyeth, Eli Lilly, GlaxoSmithKline, and Pierre Fabre; has been on the speakers bureaus of Wyeth-Ayerst, Eli Lilly, GlaxoSmithKline, and Organon and the advisory boards of Eli Lilly, GlaxoSmithKline, Organon, Wyeth-Ayerst, Forest, and Bristol-Myers Squibb; has been a consultant for Paramount Biosciences; and is a stock shareholder in Pfizer. Ms. McGahuey reports no additional financial or other relationship relevant to the subject of this article.

REFERENCES

1. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. Arch Gen Psychiatry 1977;34:98–111
2. Weissman MM, Bland R, Joyce PR, et al. Sex differences in rates of depression: cross-national perspectives. J Affect Disord 1993;29:77–84
3. Robins LN, Helzer JE, Weissman MM, et al. Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 1984;41:949–958
4. Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey, 1: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29:77–84
5. Simpson HB, Nee JC, Endicott J. First episode major depression: few differences in course. Arch Gen Psychiatry 1997;54:633–639
6. Kornstein SG. Gender differences in depression: implications for treatment. J Clin Psychiatry 1997;58(suppl 15):12–18
7. Hildebrandt MG, Stage KB, Kragh-Soerensen P. Gender differences in severity, symptomatology and distribution of melancholia in major depression. Psychopathology 2003;36:204–212
8. Leibenluft E. Gender Differences in Mood and Anxiety Disorders: From Bench to Bedside: Annual Review of Psychiatry. Washington, DC: American Psychiatric Association Press; 1999
9. Wilson IC, Rabon AM, Buffaloe WL. Imipramine therapy in depressive

syndromes: prediction of therapeutic outcome. Psychosomatics 1967;8:203–207
10. Raskin A. Age-sex differences in response to antidepressant drugs. J Nerv Ment Dis 1974;159:120–130
11. 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
12. Martenyi F, Dossenbach M, Mraz K, et al. Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: a double-blind trial of antidepressants with serotonergic or norepinephrinergic reuptake inhibition profile. Eur Neuropsychopharmacol 2001;11:227–232
13. Quitkin FM, Stewart JW, McGrath PJ, et al. Are there differences between women's and men's antidepressant responses? Am J Psychiatry 2002;159:1848–1854
14. Pinto-Meza A, Usall J, Serrano-Blanco A, et al. Gender differences in response to antidepressant treatment prescribed in primary care: does menopause make a difference? J Affect Disord 2006;93:53–60
15. Thase ME, Entsuah R, Cantillon M, et al. Relative antidepressant efficacy in venlafaxine and SSRIs: sex-age interactions. J Womens Health (Larchmt) 2005;14:609–616
16. Nishizawa S, Benkelfat C, Young SN, et al. Differences between males and females in rates of serotonin synthesis in human brain. Proc Natl Acad Sci U S A 1997;94:5308–5313
17. Ellenbogen MA, Young SN, Dean P, et al. Mood response to tryptophan depletion in healthy volunteers: sex differences and temporal stability. Neuropsychopharmacology 1996;15:465–474
18. Booij L, Van Der Does W, Benkelfat C, et al. Predictors of mood response to acute tryptophan depletion: a reanalysis. Neuropsychopharmacology 2002;27:852–861
19. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
20. First MB, Gibbon M, Spitzer RL, et al. User's Guide for the Structured Interview for DSM-IV Axis I Disorders–Research Version (SCID-I, version 2.0, February 1996 final version). New York, NY: Biometric Research, New York State Psychiatric Institute; 1996
21. Mazure CM, Nelson JC, Price LH. Reliability and validity of the symptoms of major depressive illness. Arch Gen Psychiatry 1986;43:451–456
22. Young SN, Smith SE, Pihl R, et al. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology 1985;87:173–177
23. Moreno FA, Gelenberg AJ, Heninger GR, et al. Tryptophan depletion and depressive vulnerability. Biol Psychiatry 1999;46:498–505
24. Delgado PL, Charney DS, Price LH, et al. Serotonin function and the mechanism of antidepressant action: reversal of antidepressant induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 1990;47:411–418
25. Woods SW, Charney DS, Goodman WK, et al. Carbon dioxide induced anxiety. Arch Gen Psychiatry 1988;45:43–52
26. Norusis MJ. SPSS Base System User's Guide. Chicago, Ill: SPSS Inc; 1998
27. Jones MD, Lucki I. Sex differences in the regulation of serotonergic transmission and behavior in 5-HT receptor knockout mice. Neuropsychopharmacology 2005;30:1039–1047
28. Smith KA, Morris JS, Friston KJ, et al. Brain mechanisms associated with depressive relapse and associated with cognitive impairment following acute tryptophan depletion. Br J Psychiatry 1999;174:525–529
29. Bremner JD, Vythilingam M, Ng CK. Regional brain metabolic correlates of α-methylparatyrosine-induced depressive symptoms: implications for the neuronal circuitry of depression. JAMA 2003;289:3125–3134
30. Neumeister A, Nugent AC, Waldeck T, et al. Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. Arch Gen Psychiatry 2004;61:765–773
31. McEwen BS, Alves SE, Bulloch K, et al. Clinically relevant basic science studies of gender differences and sex hormone effects. Psychopharmacol Bull 1998;34:251–259
32. Rubinow DR, Schmidt PJ. Androgens, brain, and behavior. Am J Psychiatry 1996;153:974–984
33. Kendall DA, Stancel GM, Enna SJ. Imipramine: effect of ovarian steroids on modifications in serotonin receptor binding. Science 1981;211:1183–1185
34. Schmidt PJ, Rubinow DR. Menopause-related affective disorders: a justification for further study. Am J Psychiatry 1991;148:844–852

