Gender Differences in Antidepressant Pharmacotherapy
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Mayo Clinic, Rochester

Learning Objectives
• Understanding differences in clinical appearance of depression in women compared to men.
• To review the prescription patterns in men and women at the national and international level.
• To understand the role of age dependant hormonal changes in women as a contributor to antidepressant outcome.
• To understand the impact of age on antidepressant use in women versus men.
• Conclusions-Q&A

The National Health and Nutrition Examination Survey
During 2015-2016, 8.1% of Americans aged 20 and older had depression in a given 2-week period.

Women (10.4%) were almost twice as likely as were men (5.5%) to have had depression.
The Experience of Symptoms of Depression in Men vs Women: National Comorbidity Survey Replication

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Men (N=68,458)</th>
<th>Women (N=58,313)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhedonia</td>
<td>21.4%</td>
<td>30.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inactivity</td>
<td>24.0%</td>
<td>19.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Lower energy</td>
<td>11.7%</td>
<td>14.8%</td>
<td>0.004</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12.8%</td>
<td>18.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appetite</td>
<td>12.2%</td>
<td>18.6%</td>
<td>&lt;0.001</td>
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</table>

Depression in women
- Appear to present a greater number of symptoms than men (1).
- More likely to present:
  - reverse vegetative or atypical symptoms, (increased appetite and weight gain),
  - anxiety and somatic symptoms (2).
- Tends to be more severe (3,4)
- Associated with increased functional impairment (5).
- Women are more likely to attempt suicide, but the rate of “successfully carried out” suicide is higher in men (5,6,7,8).

Antidepressant treatment for patients with major depression over the past 20 years.
Change in Antidepressants over the past 20 years.

- In 2019, 11.1% of the population was taking an antidepressant, a 15% increase from 2015.
- Women’s use of antidepressants (15.1%) was more than twice that of men’s (7.0%).
- Women 45-64 years old had the highest prevalence of antidepressant use (21.6%).
Teens (ages 13-19) experienced the greatest increase in antidepressant use up a significant 38.3%, from 5.7% to 7.9%.

The prevalence of use was higher for teenage girls (10.2%) than boys the same age (5.7%).

Common indications for all ages were: depression, anxiety, chronic pain, ODD, PTSD, eating disorders and others.

Interactions between estrogens, serotonin and norepinephrine.


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Phases of menopause and the menopause transition

Hormones and Menopausal Status as Predictors of Depression in Women in Transition to Menopause

- Depression symptoms increased during transition to menopause and decreased in postmenopausal women.
- Increased estradiol levels provided corroborating evidence that the changing hormonal milieu contributed to dysphoric mood during transition to menopause.
- Women with increasing estradiol profiles, which occur with ovarian aging in early transition to menopause, reported more depressive sx.
- Decreasing estradiol levels, which occur closer to menopause, were marginally associated with more dep sx.

Freeman et al., Arch Gen Psychiatry. 2004;61:62-70

Depressive symptoms increased during transition to menopause and decreased in postmenopausal women.

Estradiol levels across the female life cycle


The Underlying Causality of this gender difference

- Genetic, neuroanatomical, biochemical, and environmental factors (1,2).
- Gender differences in pharmacokinetics and pharmacodynamics of antidepressant medications,
  - higher plasma levels of imipramine (3,4,5) and amitriptyline (6) in women,
  - lower hydroxylation clearance of clomipramine (7).
  - an increased volume of distribution of trazodone (8).
- Specific gender effects on some peripheral markers of the serotonin transporter, such as the [3H]-paroxetine binding to human platelets, (9).
- Gender differences in overall adverse event profiles (10).
  - women respond more poorly to tricyclics compared with men (11, 12), although poorer tolerability in women may skew these efficacy results.

Dropout rates due to adverse events among men and women receiving sertraline and imipramine.

Gender differences in treatment response and remission rates to sertraline versus imipramine in patients with non-melancholic depressive disorders.

Men responded more favorably to imipramine ($B = 7.12, P = 0.005$).

Premenopausal women had a better response rate to fluvoxamine than men ($B = -8.66, P = 0.027$).

Influence of gender and menopausal status on antidepressant treatment response in depressed inpatients.

Premenopausal women had a better response than premenopausal men ($B = 14.5, P = 0.001$).
Gender Differences in Treatment Response to Sertraline Versus Imipramine in Chronic Depression

- Premenopausal women responded significantly better to sertraline than to imipramine, whereas response rates for the two drugs in postmenopausal women were similar. Among those taking imipramine, premenopausal women were significantly more likely to discontinue treatment than postmenopausal women. These findings suggest that the gender differences in imipramine response found in our study were due primarily to poor response and tolerability in premenopausal women.

Kornstein et al., Am J Psychiatry 157:9, September 2000

Age, gender, and HRT moderate response to antidepressant medications

- Table 2: Relative efficacy of TCAs and SSRIs: Ranges vary among age and sex subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>18 years</td>
<td>30%</td>
<td>40%</td>
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<td>≥50 years</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
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<td>20%</td>
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Thase et al., J Womens Health (Larchmt) 2005 Sep;14(7):609-16

Sex Differences in Antidepressant Response in Recent Antidepressant Clinical Trials

- Table 3: Sex differences in response to antidepressants

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(Thase et al., J Womens Health (Larchmt) 2005 Sep;14(7):609-16)
Sex Differences in Antidepressant Response in Recent Antidepressant Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Design</th>
<th>Intervention</th>
<th>Control</th>
<th>Measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn et al., J Clin Psychopharmacol 2005;25:318–324)</td>
<td>Men 35-55 years</td>
<td>Multiple Phase, double blind</td>
<td>Venlafaxine XR 75-300 mg (65 % W)</td>
<td>Fluoxetine 20-60 mg (61% W)</td>
<td>HAM-D17</td>
<td>Treatment outcomes did not differ on the basis of sex and menopausal status.</td>
</tr>
<tr>
<td>Kornstein et al., 2014</td>
<td>Mean Age 42-43</td>
<td>Recurrent MDD</td>
<td>Pre&amp;postmenop &amp; vs. M</td>
<td>Multiphase, double blind</td>
<td>Venlafaxine XR 75-300 mg</td>
<td>Fluoxetine 20-60 mg</td>
</tr>
<tr>
<td>Kornstein et al., 2006</td>
<td>Age 18 years or &gt;</td>
<td>MDD</td>
<td>Pooled data, 7 double blind RCT</td>
<td>Duloxetine 40-120 mg</td>
<td>M (N = 242) W (N = 484)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Young et al., 2009</td>
<td>Age 18-75 years</td>
<td>MDD</td>
<td>STAR*D Level 1 12–14 week open label</td>
<td>Citalopram (N= 2876, 63.7% female)</td>
<td>NA</td>
<td>HAM-D17</td>
</tr>
<tr>
<td>Grigoriadis et al., 2003</td>
<td>Age 40-60</td>
<td>out pts 201 (115 W, 86 M)</td>
<td>8 weeks open label flexible dose</td>
<td>SSRI (parox, citalop, fluox, sert)</td>
<td>Nefazodone Venlafaxine</td>
<td>NA</td>
</tr>
<tr>
<td>Davari-Tanha et al., 2016</td>
<td>Postmenopausal women</td>
<td>RC DB 12 wks</td>
<td>Venlafaxine 75 mg Citalopram 20 mg</td>
<td>Placebo</td>
<td>PSQI Hot flashes &amp; PSQI</td>
<td>Reduced sig. venlfxn = citalprom &lt; plcb</td>
</tr>
</tbody>
</table>

Age-dependent sex differences in the prevalence of selective serotonin reuptake inhibitor treatment: a retrospective cohort analysis (1)

- **Primary aim:** to assess the cross-sectional prevalence of antidepressant use and potential sex-related differences
- **Secondary aim:** to investigate age-dependent differences in antidepressant prescriptions by sex.

**Method:** Retrospective data analysis; Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment (RIGHT 10K), collaboration Mayo Clinic and Baylor College of Medicine, n= 11,098 individuals with previously stored DNA samples at the Mayo Clinic Biobank, Electronic health records (EHRs) within the REP, a medical records linkage system of different regional health care providers from southern Minnesota and western Wisconsin.
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• Focused on antidepressant prescriptions from REP electronic prescription data – January 2004 - August 2021
• The immediate 12-month period preceding each participant’s date of enrollment and sample donation to the biobank hereafter (enrollment year).
• Commonly used antidepressants, including monotherapy and adjunctive interventions, resulting in a list of 37 drugs of interest classified into 11 drug classes
• Inclusion was not limited to any specific diagnosis to obtain the overall prescription rates for all antidepressants.

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• Men had a gradual reduction of SSRI prescriptions as a function of age.
• Women showed a slight increase of SSRI prescriptions until approximately 50 years of age.
• Prescriptions began a gradual decline following age 55.
• The maximum difference in estimated probability of prescription by age occurred at 55 years (Prob(M) = 0.084, Prob(F) = 0.169, Diff = 0.085).
• The only class for which we did not observe prescriptions decline with age at any point in time were TCAs in women.

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Conclusions

• Women are at higher risk for developing depression compared to men.
• The increased risk appears to be associated with reproductive "windows of vulnerability" (1).
• The association between reproductive milestones and depression in women suggests a contributing role of sex hormones (i.e., estrogen) to mood regulation.
• Animal data and clinical studies support the notion that estrogen has important modulatory effect on serotonin activity.

## Conclusions

- Antidepressant treatment outcome shows age-sex interaction.
- Females are better responders to SSRI’s at premenopausal years vs. postmenopausal years.
- Males are more stable in response and side effects to antidepressants.
- Further studies are needed to understand the effect of age- and sex-dependent patterns of antidepressant use in the context of reproductive health and specific indication for prescription.