


SSRIs and Women's Mental Health

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Gender Differences

- Biological: reproductive system function, brain structure and function, drug interactions
- Psychosocial and behavioral factors of gender
- Age-related differences
- Racial differences


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Life Phases

- Pre-pubescent
- Puberty
- Reproductive years/premenopausal
- Menopausal transition
- Post-menopausal


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Reproductive System Function

- Cycling sex hormones
 - estrogen
 - progesterone
 - testosterone
- Exogenous hormones (OCs and HRT)
- Pregnancy
- Menopause


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Timing of Fluctuations in Sex Hormones

- Pulsatile (minutes to hours)
- Circadian (diurnal)
- Infradian (near-monthly)
- Circannual (seasonal)

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Estrogen

- Modulates serotonin: mood, sleep, appetite, migraines, concentration/memory
- Uterine lining/atrophy
- Hot flashes
- Verbal memory/neuronal growth

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Progesterone

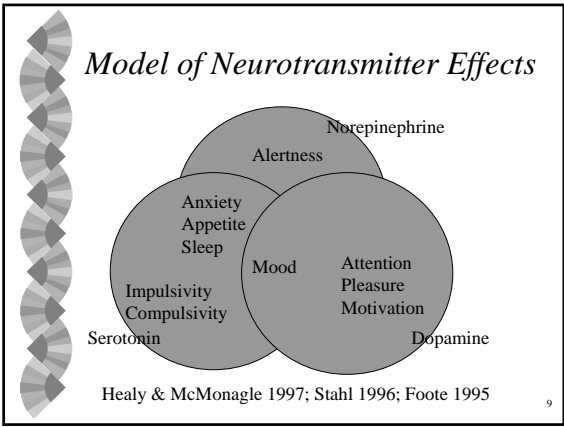
- Lowers mood
- Decreases anxiety
- Initiates menstrual bleeding

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Testosterone

- Increases sex drive
- Vitality/energy

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Pharmacodynamics: Neurotransmitters

| Neurotransmitter | Estrogen | Progesterone |
|------------------|------------------------|----------------------|
| Serotonin | + levels 5-HT & 5-HIAA | |
| GABA | + GABA-A | agonist |
| Dopamine | + release + MAO-B | + release + MAO-A |

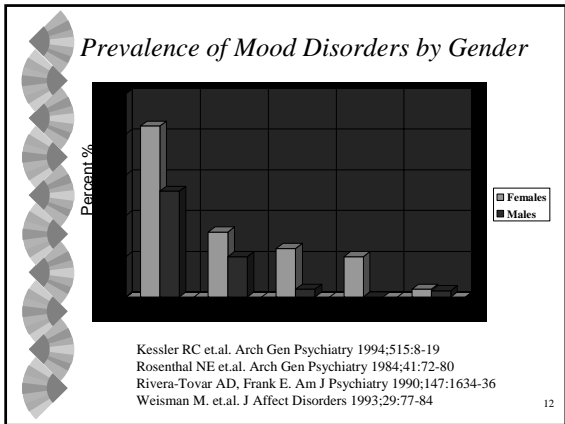
Majewska in Jensvold, Halbreich, & Hamilton 1996

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Drug Interactions

- Sex hormones in women increase blood levels of most medications (except during pregnancy)
- Oral contraceptives may change blood levels of some drugs/some drugs may render OCs ineffective
- Some women need medication increases premenstrually

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Clinical Presentation

- Association with reproductive-life events
- Atypical features common
- Increased risk of seasonal pattern
- Frequent psychiatric and medical comorbidity
- Course of illness more likely to be chronic or recurrent

DSM-IV; Benazzi 1999; Schlager 1993; Maier & Falkai 1999; Kornstein 1997

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Reproductive-life Events Associated with Mood Disorders

- Late luteal phase (premenstrual)
- Postpartum period
- Menopausal transition
 - 5 years on either side of menopause
 - Onset of irregular menses
 - FSH level >30 ml units/ml on cycle day 2
- Hormonal therapies (OCs and HRT)

Hendrick 1996; Altshuler 1998; Avis 1994; Burt 1997

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Premenstrual Dysphoric Disorder

- Cyclic occurrence of symptoms premenstrually, not present by the end of the menstrual period – need to differentiate from premenstrual exacerbation of depression
- Severe mood symptoms associated with functional impairment (2-9% of women)
- Associated with major depressive disorder

DSM-IV 1994; Hendrick 1996

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Premenstrual Dysphoric Disorder

- Onset mid- to late 20s - worsens with age to the menopause
- Possible link to serotonin dysregulation
- Treat with SSRIs either continuously or intermittently (luteal phase) – may improve tolerability

Clayton 1998; PDR 2003

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Depression During Pregnancy

- Usually with prior history of depression (incidence 10%)
- Risks to consider:
 - Untreated illness in mother
 - Medication exposure to the fetus
 - Organ malformation
 - Neonatal toxicity or discontinuation syndromes after delivery
 - Long-term neurobehavioral sequelae
 - Relapse with D/C of maintenance therapy
 - Undesirable obstetrical outcomes: preterm delivery, low birth weight, small for gestational age

Kelly 2001; Nonacs 2002; Orr 2002; Steer 1992

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Management of Depression During Pregnancy

- Minimize fetal exposure to depressive illness and to medication
- Treatments:
 - Psychotherapy (IPT, CBT)
 - Antidepressants
 - No known teratogenic effects
 - Utilize medications previously effective for the woman (may need higher dose while pregnant)
 - Electroconvulsive therapy

Nonacs 2333; Stowe 2001; Miller 1994

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Postpartum Depression

- Maternity blues: occurs postpartum days 3-14 (75% of women)
- Postpartum depression: MDD beginning within 4 weeks postpartum (8-15% of women)
- Puerperal psychosis: usually bipolar illness or MDD with psychotic features (1:1000 women)

DSM-IV 1994; Yonkers & Chantilis 1995

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Postpartum Depression

- 60% with index episode of MDD
- Risk factors
 - Prior history of MDD (30% chance)
 - Depressive symptoms during pregnancy (35% incidence)
 - History of postpartum depression (>50% likelihood)
 - Problematic couples relationship
- Symptoms may be subtle

Cox 1982; O'Hara 1991; O'Hara 1995

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Treatment of Depression in the Postpartum

- Psychotherapy (IPT, CBT)
- Antidepressants
 - Breastfeeding exposes the infant to the antidepressant
 - Treat to remission
 - Treat conservatively - full 12 months
- Mood stabilizers for BPAD

Stowe 2001; Nonacs 1998

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Depression and the Menopausal Transition

- Risk period begins 5 years prior to cessation of menses
- Biological risk factors: prior history of depression, surgical/chemical menopause, early or long perimenopausal period, higher FSH levels; severe vasomotor symptoms
- Cultural, social and family factors

Kessler 1993; Burt 1998; Harlow 1995; Hay 1994; Koster 1993; Huerta 1995; Velasco 1990; Ballinger 1990; Soares 2003

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Overlap of Symptoms of the Menopausal Transition and MDD

Clayton A. *Primary Psychiatry*, Vol 10, No 4, 2003


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Considerations in Treatment of MDD in the Menopausal Transition

- Antidepressant therapy not systematically studied considering menopausal status
- Some improvement in depressive symptoms seen with stabilization of sex steroids (HRT) +/- antidepressants
- SSRIs may reduce vasomotor symptoms with further improvement in MDD outcome and QOL

Joffe 2003; Soares 2001; Soares 2003; Kaufert 1998

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Atypical Features

- Symptoms: mood reactivity, hypersomnia, hyperphagia or weight gain, rejection sensitivity, leaden paralysis
- Common in Seasonal Affective Disorder (SAD) where 80% are women
- May respond better to noradrenergic agents

DSM-IV 1994

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Comorbid Conditions

| Psychiatric Conditions | Medical Conditions |
|--|---|
| <ul style="list-style-type: none"> • Anxiety disorders • Somatoform disorders • Eating disorders • Borderline personality disorder • Sexual disorders | <ul style="list-style-type: none"> • Thyroid disorders • Migraines • Fibromyalgia • Irritable bowel syndrome • Obesity |

Maier & Falkai 1996; French 1999; Franko 1999; McCarthy 1990

Pop 1998; Couch 1975; Offenbaecher 1998; Averill 1996; Hudson & Pope 1990

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Commonalities

- Epidemiologic association/co morbidity (bidirectional)
- Pathophysiologic similarities
- More prevalent in women
- Each disorder has both psychological and medical components
- Similarities in pharmacologic response to medications with effects on serotonin function


Hudson 1990

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Epidemiologic Evidence For Linkage

| | Depression | Migraine | IBS | Obesity | Pain D/Os | SD |
|--------------------------|------------|----------|-----|---------|-----------|----|
| Depression | | ++ | ++ | ++ | ++ | ++ |
| Migraine | ++ | | + | | + | |
| IBS | ++ | + | | | + | + |
| Obesity | ++ | | | | + | + |
| Pain D/Os (fibromyalgia) | ++ | + | + | + | | + |
| SD | ++ | | + | + | + | |

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Common Physiologic Abnormality Links Disorders

- Hypofunctional central 5-HT system (low serotonin tone or blunted 5-HT responsiveness)
- HPA axis hyperactivity
- 5-HT abnormality may contribute to the HPA abnormality
- Chronobiology: Disorders associated in time with changes in sex steroids (increased or decreased sensitivity to modulation of 5-HT and/or hypothalamic-pituitary-end-organ axis by changes in hormones, particularly estrogen?)


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Pharmacologic Evidence For Linkage

| Disorder | Estrogen | | | | |
|--------------|------------------|------------------|------------------|-------------------|---|
| | TCAs | SSRIs | SNRIs (in women) | MAOIs | Others |
| Depression | + | + | + | + | + |
| Migraine | + ^{1,3} | + ^{1,3} | | + ⁴ | + ¹ Triptans ^{1,5} |
| IBS | + ⁶ | + ^{1,6} | | | |
| Obesity | - | + ^{7,8} | | - | 5-HT ^{7,8} releasers & receptor agonists |
| SD | - | - | 2,9 | - | 3,9 |
| Fibromyalgia | | | | +/- ¹⁰ | - ¹¹ |
| | | 12,13 | 12,13 | | + ¹⁴ |

1. Gruber AJ et al. *Psychiatr Clin North Am.* 1996;19:351-369. 2. de Novaes Soares C et al. *Arch Gen Psychiatry.* 2001;58:529-534. 3. Tomkins GE et al. *Ann J Med.* 2001;111:54-63. 4. Somerville BW. *Neurology.* 1972;22:355-365. 5. Miranda H et al. *Headache.* 2001;41:680-684. 6. Farthing MJ. *Best Pract Res Clin Gastroenterol.* 1999;13:461-471. 7. Boushaki FZ et al. *Clin Endocrinol.* 1997;46:461-466. 8. Rosmond R, Bjornorp P. *Metabolism.* 1998;47:1167-1193. 9. Clayton AH et al. *J Clin Psychol.* 2002 (in press). 10. Sherwin B. *Annu Rev Sex Res.* 1991;2:161-198. 11. Socaves RT. *J Clin Psychiatry.* 1992;102:4-10. 12. Arnold LM et al. *Psychosomatics.* 2000;41:104-113. 13. O'Malley PG et al. *J Gen Intern Med.* 2000;15:659-666. 14. Waxman J, Zatskis SM. *Postgrad Med J.* 1988;60:165-171.



Available Interventions for MDD

- Healthy lifestyle: exercise, vitamin supplements, reduce caffeine and alcohol
- Pharmacotherapy
- Light therapy
- Psychotherapy
- Electroconvulsive therapy (ECT)
- Combination therapy

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Treatment Considerations

- Comorbidity
- Potential drug-drug interactions
- Effects of sex steroids on underlying condition and pharmacokinetics
- Differential therapeutic and adverse effects of medications
- Augmentation strategies
- Long-term tolerability

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Antidepressant Tolerability

- SSRIs and MAOIs better tolerated than tricyclics in premenopausal women
- Long-term side effects of importance (class-effect of SSRIs):
 - sexual dysfunction
 - weight gain
 - cognitive blunting
- Coexisting disorders affect tolerability (particularly comorbid anxiety)

Kornstein 1997; Raskin 1974; Steiner 1993

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Augmentation Strategies to Achieve Full Remission

- HRT
- Thyroid
- Second antidepressant (bupropion, mirtazapine)
- Psychotherapy
- Mood stabilizer (lithium)
- Psychostimulants
- Atypical antipsychotics
- Pindolol

Schneider 1997 & 1998; Frye 1997; Joffe 1998; Clayton 2002; Nelson 1998; Rouillon & Gorwood 1998; Dietrich & Emrich 1998; Nelson 2002


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Principles of Medication Treatment in Women

- Lower doses used in women than in men except during pregnancy
- Premenstrual effects vary with the individual
- OCs may interact with other medications
- Counsel reproductive-age women about potential medication effects during pregnancy

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Pharmacotherapy for MDD in Women

- Co-morbidities complicate medication therapy
- Newer antidepressants are better tolerated than TCAs with a greater therapeutic response
- Norepinephrine active agent useful with atypical symptoms
- Augmentation strategies may be needed for full remission of symptoms
- Long-term side effects important in chronic or recurrent depression

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Conclusions

- Women have higher rates of depression
- Chronobiology important in episode onset
- Physiological substrate of sex differences influences psychopathology, medication management, and treatment outcomes
- Factors complicating diagnosis and treatment include atypical symptoms, comorbidity, and differential response
- Long-term tolerability of antidepressant medication is important in women

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Dr. Anita Clayton – Questions & Answers

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