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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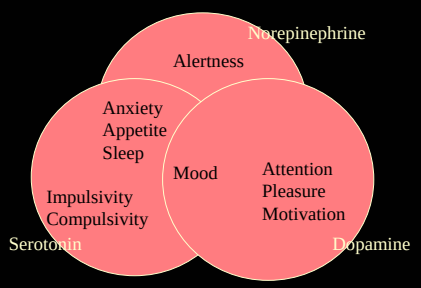
Model of Neurotransmitter Effects



Healy & McMonagle 1997; Stahl 1996; Foote 1995

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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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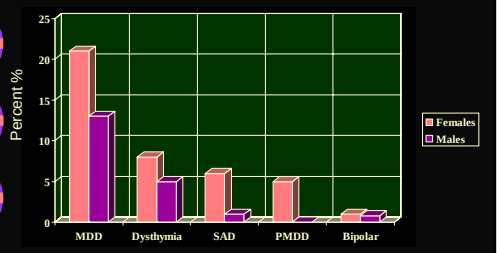
Prevalence of Mood Disorders by Gender



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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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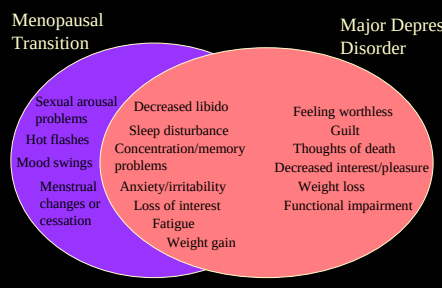
Overlap of Symptoms of the Menopausal Transition and MDD



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
• Anxiety disorders • Somatoform disorders • Eating disorders • Borderline personality disorder • Sexual disorders	• 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	++		+	+	+	

Clayton 2003

Common Physiologic Abnormality Links Disorders

- Hypofunctional central 5-HT system (low serotonin tone or blunted 5-HT responsivity)
- 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	TCAs	SSRIs	SNRIs	Estrogen (in women)	MAOIs	Others
Depression	+ [1]	+ [1]	+ [1]	+ [2]	+	
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]	+/– [10]	- [11]	
Fibromyalgia	+ [12,13]	+ [12,13]		+ [14]		

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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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