Use of Psychotropics in Women of Childbearing Age

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Objectives

- Review the incidence of affective disorders in pregnancy and the post-partum period
- Discuss the risks of untreated mental illness during pregnancy and the post-partum period

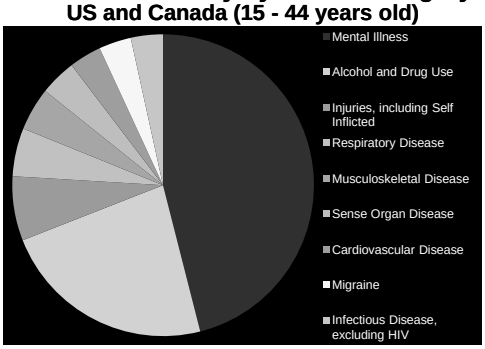
Objectives

- Evaluate the risks and benefits of individual psychotropic drug classes in pregnancy and lactation
- Provide counseling recommendations for the pregnant or lactating patient

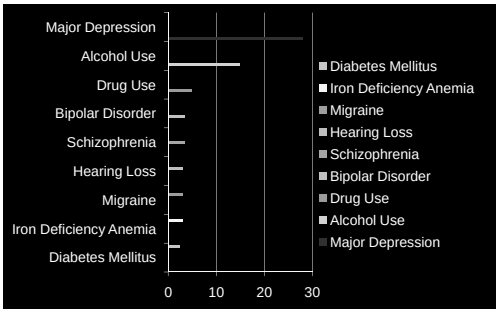
Depression in Women

- Higher rates of depression occur in women compared to men in all age groups over age 10 years old
- Lifetime prevalence rates:
  - Women 21.3% (12.7% men), most pronounced prior to age 45 years of age
  - Women have approximately 2 times the risk compared to men

Cause of Disability by Illness Category
US and Canada (15 - 44 years old)



Causes of Disability by Specific Illness



Pregnancy

- 82% of US women have children
  - By age 44 per census data for 2002
- 50-60% of pregnancies are unintended or mistimed
- Two-thirds of American women will have at least one unintended pregnancy in their lifetimes

Depression in Pregnancy

- Common problem
  - 10-15% of women experienced significant depressive symptoms during pregnancy
- Serious risks
  - Untreated depression may negatively affect maternal weight gain and birth weight and increase the risk of prematurity

Depression in Pregnancy

- Lack of data for drug interventions
  - No published studies of antidepressant efficacy in pregnancy

Depression During Pregnancy

- May negatively affect maternal weight gain
- Increases risk of low birth weight, prematurity and small for gestational age

Depression During Pregnancy

- Anxiety, stress in pregnancy increase risks of:
  - Preeclampsia, preterm delivery, reduced birth weight and head size
  - Poorer psychomotor development and adaptation to new environments in infants

Depression During Pregnancy

- Newborns cry more, are more difficult to soothe if mothers were anxious or depressed in pregnancy

Depression During Pregnancy: Medication

- FDA ratings
  - A – Studies in humans show no risk
  - B – No evidence of risk in humans
    - If no human data, animal data shows no risk

Depression During Pregnancy: Medication

- C – Risk cannot be ruled out
- D – Positive evidence of risk
- X – Contraindicated in pregnancy

Antidepressants During Pregnancy

- Generally studies show lack of association between TCAs, SRIs, and major malformations or prematurity
  - Kulin et al., JAMA 1998, Ericson et al., 1999

Antidepressants During Pregnancy

- Some studies show greater risk of minor malformations, neonatal complications with fluoxetine exposure
  - Chambers et al., 1996, Pastuszak et al., 1993

Antidepressants During Pregnancy

- Paroxetine has new prescribing language concerning increased risk of cardiovascular malformation with 1st trimester use (FDA 2005)
  - FDA labeling change from 'C' to 'D'

Perinatal Depression

- Non-medication treatments
  - ECT (Miller, 1994)
  - Psychotherapy (Spinelli, 1997)
  - Light Therapy (Oren et al., 2002)
  - Omega-3 fatty acids (Freeman et al., 2006)

Pharmacological Treatments for Acute Post-partum Depression

- Fluoxetine-double-blind, placebo-controlled, N=87 (Appleby et al., 1997)
- Estrogen-double-blind, placebo controlled, N=61 (Gregoire et al., 1996)

Pharmacological Treatments for Acute Post-partum Depression

- Paroxetine-Misri et al., 2004, N=35, all received paroxetine, half randomized to CBT
- Sertraline-open-label, Stowe et al., 1995, N=21
- Venlafaxine-open-label, Cohen et al., 1997, N=19

Pharmacological Treatments for Acute Post-partum Depression

- Fluvoxamine-open-label, Suri et al., 2001, N=6
- Bupropion-open-label, Nonacs et al., 2005, N=8
- Sertraline vs. Nortriptyline-Wisner et al., 2006, N=20

Antidepressant Treatment During Breastfeeding

- Most studies of a breastfeeding infant's exposure to antidepressants show low levels of drug in breast milk and infant serum
- Few case reports of adverse effects
  - Doxepin
    - Infant had clinical effects of vomiting, sedation (Frey 1996)

Antidepressant Treatment During Breastfeeding

- Fluoxetine
  - Case report of high infant blood levels, colicky symptoms (Lester 1993)
- Citalopram
  - Sleep trouble in infant (Schmidt 2000)

Antidepressant Treatment During Breastfeeding

- Nefazodone
  - Case report of drowsiness, lethargy, inability to maintain body temp in a premature baby (Yapp, 2000)
- Bupropion
  - Possible seizure in an infant (Chaudron, 2004)

Antidepressant Treatment During Breastfeeding

- Tricyclic antidepressants
  - Doxepin
    - 9 day old infant had clinical effects
      - Vomiting
      - Sedation

Antidepressant Treatment During Breastfeeding

- No adverse clinical effects reported with other TCAs
- Very low levels or no accumulation for other TCAs
  - Nortriptyline
  - Amitriptyline
  - Clomipramine

SSRIs and Breastfeeding

- Fluoxetine
  - Taddio et al., 1996
    - N=10
    - 10% of maternal dose excreted into mild
    - No adverse effects

SSRIs and Breastfeeding

- Yoshida et al., 1998
  - N=4
  - Detectable in milk
  - Non-detectable in infant serum and urine
  - No adverse effects

SSRIs and Breastfeeding

- Kristensen et al., 1999
  - N=14
  - Mean total infant exposure was 6.81% of maternal dose
    - Individual variability

SSRIs and Breastfeeding

- Lester et al., 1993
  - Case report of high infant blood levels
  - Colicky symptoms

SSRIs and Breastfeeding

- Chambers et al., 1999
  - In women who took fluoxetine during pregnancy, followed postpartum while nursing

SSRIs and Breastfeeding

- N=26 on meds vs N=38 not on medications
  - Infants breastfed by mothers on fluoxetine demonstrated growth curve significantly lower than controls
    - 2 weeks-6 months

SSRIs and Breastfeeding

- Sertraline
  - Kristensen et al., 1998
    - N=8 present at low levels in milk
    - N=4-non detectable in infant plasma
    - No adverse effects

SSRIs and Breastfeeding

- Wisner et al., 1998
  - N=9-1 infant had high levels of sertraline and metabolites in serum
  - Most had low levels of sertraline and metabolites
  - No adverse effects

SSRIs and Breastfeeding

- Stowe et al., 2003
  - N=26
    - 22 pairs maternal and infant sera obtained
    - No adverse effects
  - Highest concentrations in hind milk
    - 8-9 hours after ingestion

SSRIs and Breastfeeding

- Sertraline detectable in N=4 babies (18%)
- Desmethylsertraline detectable in 11 (50%)
- Calculated infant doses represented 0.54% of maternal dose

SSRI's and Breastfeeding

- Citalopram
  - Schmidt et al., 2000
    - N=1
      - Detectable in mild and infant serum
      - Infant serum level was 12.8% of maternal serum level
        - Sleep trouble in infant

SSRI's and Breastfeeding

      - Resolved after decreasing maternal dose, substituting formula
  - Spigset et al., 1997
    - N=3
      - Dose in mild
      - 1.8% of maternal dose

SSRI's and Breastfeeding

  - Rampono et al., 2000
    - N=7
      - Dose in milk
      - 4-5% (combined with metabolite) low
      - No adverse effects
      - Serum levels detectable in 3 infants

Other Antidepressants and Breastfeeding

- Bupropion
  - Briggs et al., 1993
    - N=1 (14 month old)
      - Accumulation in breastmilk
      - Not detected in plasma sample
      - No clinical effects

Other Antidepressants and Breastfeeding

  - Baab et al., 2002
    - N=2 (17 weeks old)
      - Not detectable in infant serum
      - No clinical effects
  - Chaudron and Schoenecker, 2004
    - Possible infant seizure

Other Antidepressants and Breastfeeding

- Venlafaxine, O-desmethylvenlafaxine (OVD)
  - Ilett et al., 1998
    - Found in milk
      - 7.6% of maternal plasma level
    - Metabolite detectable in infants
      - N=3, no clinical effects

Other Antidepressants and Breastfeeding

- Hendrick et al., 2001
  - Venlafaxine not detectable in infants
  - Metabolite detectable
    - N=2, no clinical effects

Other Antidepressants and Breastfeeding

- Illett et al., 2002
  - Concentrations in breastmilk (Venlafaxine and desvenlafaxine) were 2.5-2.7 times the maternal dose

Other Antidepressants and Breastfeeding

- Low levels detected in infants
  - 1 of 7 detectable venlafaxine
  - 4 of 7 detectable ODV
  - N=7, no clinical effects

Treatment Recommendations: Perinatal Depression

- Moderate to severe depression: Treat!
  - Consider role of antidepressants
  - Discuss risks and benefits with mother
- Use of lowest effective doses
- Consultation with experts

Treatment Recommendations: Perinatal Depression

- Mild depression
  - Consider non-medication alternatives

Treatment of Depression in Pregnancy and Postpartum

- Wish list
  - Efficacy
  - Safety in pregnancy
  - Safety in breastfeeding
  - Babies and moms need this anyway
  - No carbs
  - Tastes like chocolate

Omega-3 Fatty Acids and Supportive Psychotherapy

- Two pilot studies of omega-3 fatty acids found good tolerability and efficacy for MDD in pregnant and postpartum women
- Omega-3 fatty acids are well established for there health benefits for mothers and babies

Omega-3 Fatty Acids and Supportive Psychotherapy

- Many women prefer non-medication treatment options during pregnancy and breastfeeding

Background and Methods

- Study of omega-3 fatty acids vs. placebo for depression during pregnancy and postpartum
  - Randomized to eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), 1.9 g/day, or placebo for eight weeks

Background and Methods

- All participants received supportive psychotherapy
- N=59 participants enrolled

Results

- Omega-3 fatty acids well tolerated
- Participants in both groups experienced significant decreases in EPDS and HAM-D scores ($p<0.0001$) from baseline
- No benefit of omega-3 fatty acids over placebo
  - All received supportive psychotherapy

Conclusions: Omega-3 Fatty Acids

- Difficult to assess the efficacy of omega-3 fatty acids definitively
  - Small study, omega-3 give in addition to psychotherapy
  - Appropriate dose is not yet known

Conclusions: Omega-3 Fatty Acids

- Although randomly assigned to omega-3 vs. placebo, those who received omega-3 fatty acids had a significantly higher number of previous antidepressant trials
  - More recurrent course of MDD?

Conclusion: Psychotherapy

- Provides preliminary data regarding supportive psychotherapy for perinatal depression
- Supportive psychotherapy
  - Designed to be easy to implement
  - Flexible to accommodate the schedules of women with infants and small children

Conclusion: Psychotherapy

- Cost-effective
- Provide additional safety monitoring
- There is an urgent public health need for safe, easy to deliver, and cost effective treatments for perinatal depression

Summary

- Risk/benefit decisions in pregnancy and breastfeeding are complicated
- Must be tailored to the individual
- Untreated mood and anxiety disorder have negative consequences for a woman, her children and the entire family
  - Must compare relative risks of medication to untreated disorders

Summary

- Women need and deserve more evidence based treatment information

Treatment of Bipolar Disorder in Women

Objectives

- Identify the clinical course of bipolar disorder during the reproductive life cycle in women
  - Menstrual cycle, pregnancy, post-partum period and menopause
- Describe the pharmacotherapy issues relevant to women during the childbearing years
  - Pregnancy, lactation, postpartum mood

Objectives

- Detect treatment issues and pharmacotherapy options during perimenopause in women with BPD
- Discuss the management of osteoporosis in women with bipolar disorder

Questions to Ask Yourself

- Does the patient have a bipolar spectrum disorder?
- Might this patient become pregnant during her treatment?
- What are the risks of the mood stabilizer(s) to a baby?
  - In utero, breastfeeding

Questions to Ask Yourself

- What are the implications of reproductive events-pregnancy, postpartum, menstrual cycle, peri-menopause?

Does the Patient Have Bipolar Spectrum Disorder?

- Bipolar disorder is often a missed diagnosis
- Women often present with bipolar depression-need to take a careful history to assess for bipolar disorder
- Hypomania may be easy to overlook

Question

- According to the NDMDA, what percentage of patients consulted three or more providers before receiving an accurate diagnosis of bipolar disorder?
  - 18%
  - 38%
  - 28%
  - 48%

* NDMDA = National Depressive and Manic Depressive Association. Lish, et al., 1994.

Bipolar Disorder in Women

- Women experience more rapid-cycling
- More mixed episodes
- More depressive symptoms
- Later age of onset
- More Bipolar II
- More comorbidity

Bipolar Disorder in Women

- Less likely than men to have legal problems
  - Leibenluft 1996, 1997; Goodwin and Jamison 1990; Angst et al., 1978; Roy-Byrne et al., 1986; McElroy et al., 1995; Baldassano, et al., 2005

Treatment Response

- No evidence of gender difference in response to mood stabilizers
- More antidepressant-induced rapid cycling
- Differences in side effects
  - Lithium treatment – more hypothyroidism and weight gain in women
    - Altshuler, et al., 1995, Henry 2002.

Effects of Reproductive Cycle

- Menstrual cycle
- Pregnancy and postpartum
- Perimenopause
- Medication issues in fertility/infertility

Menstrual Cycle

- May be exacerbation of symptoms premenstrually or menstrually for some women
  - Case reports, retrospective data
  - 66% reported regularly occurring exacerbations
  - 25% reported premenstrual depressive syndrome, increased anxiety

Menstrual Cycle

- Prospective study-inconsistent findings
- Meds for PMDD may precipitate mania
  - SSRIs, alprazolam, buspirone
    - Blehar, et al., 1998; Roy-Byrne, et al., 1985; Leibenluft et al., 1999; Ragson, 2003.

Pregnancy and Postpartum Issues

- Pregnancy
  - Risks of medications in pregnancy
  - Risks of discontinuation of medication
- Postpartum
  - High risk of relapse
  - Medications and breastfeeding

Pregnancy and Postpartum: Risk of Discontinuing Medications

- Viguera, et al., 2000
  - Retrospective comparison of recurrence rates
    - Pregnant (N=42) vs. nonpregnant women (N=59) with bipolar disorder

Pregnancy and Postpartum: Risk of Discontinuing Medications

- Rates of recurrence after discontinuation of medication
  - Similar for pregnant and nonpregnant women, except more depressive episodes in pregnant women
    - Overall recurrence rate =55%

Pregnancy and Postpartum: Risk of Discontinuing Medications

- Women at increased risk of recurrence postpartum
  - 70% vs. 24%
  - 2.9 x more likely to have recurrence than nonpregnant women after same time course

Pregnancy and Postpartum: Risk of Discontinuing Medications

- Recurrence risk greater after rapid discontinuation (<2 weeks) than gradual (2-4 weeks)

Bipolar Disorder: Course During Pregnancy

- Viguera, et al., 2007
  - 89 pregnant women with bipolar I or II followed through pregnancy
    - Enrolled by 24 weeks gestation, euthymic for at least one month prior to conception, either continued or discontinued mood stabilizers for the pregnancy

Bipolar Disorder: Course During Pregnancy

- 70.8% relapsed into a mood episodes during pregnancy
- Women who discontinued medication were more likely to experience recurrences (85.5% vs. 37%) and spend more time ill

Bipolar Disorder: Course During Pregnancy

- Rapid mood stabilizer discontinuation associated with higher risk of recurrence
  - RR=1.4, p=0.008
- Unplanned pregnancy associated with greater risk of recurrence
  - RR=1.5,p=0.006

Postpartum: Natural Course

- Structured interviews about lifetime course of bipolar disorder in women and impact of reproductive events
  - N=50 women
- Onset of bipolar disorder was early in many
  - 32% had onset of mood episodes prior to menarche

Postpartum: Natural Course

- Of the women with children
  - 67% had postpartum episodes
    - Almost exclusively depressive
  - Recurrence rates of postpartum depression were 64%

– Freeman, et al., 2001

Postpartum Psychosis

- Rare (0.1-0.2%) in general after childbirth
- Onset usually within 1-2 weeks after delivery
  - Generally includes agitation, irritability, sleep disturbance

Postpartum Psychosis

- Suspect bipolar disorder
  - Women with bipolar at risk
  - Clustering in families
    - Nonacs and Cohen 1998; Jones and Craddock 2001

Risks of the Untreated Disorder in Pregnancy

- Estimated baseline rate of major malformations in the US is 3-4%
- Alcohol and tobacco use prevalent in patients with bipolar disorder
  - Both are teratogenic and can complicate the pregnancy

Risks of the Untreated Disorder in Pregnancy

- Untreated depression and mania carry risks for mother and baby
  - Nonacs and Cohen 2002; King and Fabro 1983

Medication During Pregnancy

- FDA ratings
  - A – Studies in humans show no risk
  - B – No evidence of risk in humans
    - If no human data, animal data show no risk

Medication During Pregnancy

  - C – Risk cannot be ruled out
  - D – Positive evidence of risk
  - X – Contraindicated in pregnancy

Mood Stabilizers in Pregnancy

- Lithium: First trimester-risk of cardiovascular malformations
  - Ebstein's anomaly: 0.1-0.2% (RR 10-20)
  - Risk ratio for cardiac malformations is 1.2 -7.7 and the risk for Epstein's anomaly rises from 1/20,000 to 1/1,000

Mood Stabilizers in Pregnancy

- Risk of neural tube defects
  - Valproate (1-5%)
  - Carbamazepine (0.5-1%)
    - Yonkers et al., 2004; Newport at el., 2005

Mood Stabilizers in Pregnancy

- Lithium
  - Complicated by maternal glomerular filtration rate (GFR) changes during pregnancy
  - Excreted more rapidly
    - May need to increase dose

Mood Stabilizers in Pregnancy

- After delivery GFR decreases rapidly
  - Should follow lithium levels during labor and delivery
  - Adjust dose as needed

Mood Stabilizers in Pregnancy

- Anticonvulsants
  - Risk of craniofacial abnormalities, autism, other neurodevelopmental problems

Mood Stabilizers in Pregnancy

- Lithium
  - "Floppy baby"-cyanosis, hypotonicity, lethargy, cardiac murmurs, arrhythmias, respiratory distress, nontoxic goiter, hypothyroidism, nephrogenic diabetes insipidus

Lamotrigine in Pregnancy

- Pregnancy increased lamotrigine clearance by >50%
  - Returns to baseline after delivery
- Association with oral clefting
  - North American Antiepileptic Drug Pregnancy Registry; 5 of 564; first trimester exposures rate of 8.9 per 1,000; compared with 0.37 in general population

Lamotrigine in Pregnancy

- First trimester birth defects more likely with anticonvulsant polypharmacy (International Lamotrigine Pregnancy Registry)
  - 3/168(1.8%) with monotherapy
  - 5/50 (10%) lamotrigine and valproate

– Myllynen, et al., 2003. Tran et al., 2002

Atypical Antipsychotics in Pregnancy

- Prospective study of outcomes after first trimester exposure to:
  - Olanzapine (N=60)
  - Risperidone (N=49)
  - Quetiapine (N=36)
  - Clozapine (N=6)
  - Comparison with controls (no exposure)

Atypical Antipsychotics in Pregnancy

- Exposed women had higher rates of factors that increase risks to pregnancy
  - Unplanned pregnancy, did not take vitamins/folate, smoking, less education

– McKenna, et al., 2005

Atypical Antipsychotics in Pregnancy

- High rates of polypharmacy-concurrent conventional antipsychotics (16%)
  - Antidepressants (57%)
  - Anticonvulsants (17%)
  - Benzodiazepines (34%)
  - Lithium (6%)

Atypical Antipsychotics in Pregnancy

- Diagnoses
  - Depression (29%)
  - Bipolar disorder (18%)
  - Schizoaffective disorder (12%)
  - Psychotic episodes (7%)
  - OCD (2%)

Atypical Antipsychotics in Pregnancy

- PTSD (1%)
- Schizophreniform disorder (1%)
- Some women reported concurrent diagnoses and some women did not know their diagnoses

– McKenna, et al., 2005

Atypical Antipsychotics in Pregnancy

- Rates of malformations did not differ between groups exposed to atypicals and control group (0.9% vs. 1.5%)
- No significant difference between labor complications or neonatal complications

– McKenna et al., 2005

Antidepressants During Pregnancy

- Generally studies show lack of association between TCAs, SSRIs and major malformations or prematurity
- Some studies – great risk of minor malformations, neonatal complications with fluoxetine exposure

Antidepressants During Pregnancy

- Paroxetine – new language on prescribing information concerning increased risk of cardiovascular malformation with first trimester use
- SSRIs in late pregnancy and persistent pulmonary hypertension of the newborn (PPHN)

Antidepressants During Pregnancy

- Reports of suspected neonatal withdrawal or toxicity syndromes, complications after in utero exposure to SSRIs

– Kulin, et al., 1998; Ericson et al., 1999; Chambers 1996; Pastuszak 1993; Chamber 2006; Moses-Kolko 2005

Pregnancy

- Ultrasound – Level II
  - Cardiac (18-20 weeks)
  - Spina bifida (18-20 weeks)
- Fetal echocardiography

– Jacobson 1992

Neural Tube Defects

- Folate supplementation
  - 4 mg/day
  - Starting one month prior to conception

– McDonald, et al., 2003

ECT

- May be helpful in depression, mania, psychosis during pregnancy
- No known adverse effects in offspring

– Miller 1994

Take Home Points: Bipolar Disorder and Pregnancy

- Women with bipolar disorder are likely to need treatment with mood stabilizers through the reproductive years
- Health care providers need to anticipate women with bipolar disorder may experience pregnancies, planned or unplanned, while being treated

Take Home Points: Bipolar Disorder and Pregnancy

- Unplanned pregnancies should be anticipated
- Routine treatment planning for women should include discussion about risks/benefits of medication during pregnancy, even if a pregnancy is not planned

– Freeman 2007

Postpartum Treatment

- Prescribe sleep
  - Sleep deprivation
    - Similar to antidepressants regarding risk of induction of mania/hypomania (10%)

Postpartum Treatment

- Prescribe support
  - Good social support associated with quicker recovery, less symptomatic
  - Better prophylaxis against episodes

– Colombo et al., 1999; Johnson et al., 1999; Stefos et al., 1996

Mood Stabilizers and Breastfeeding

- Lithium
  - Toxicity reported in cases with infant serum levels at 0.1-0.5 times the maternal level
  - Contraindicated at one time by the American Academy of Pediatrics

Mood Stabilizers and Breastfeeding

- Revised to classification "Drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution."

– American Academy of Pediatrics 2001

Mood Stabilizers and Breastfeeding

- Lithium and Breastfeeding: Recent report
  - N=10 mother baby pairs
    - Mother's stable, lithium 600-1,200 mg daily
    - Babies' serum levels 0.09-0.3 MEq/L (average 0.16)

Mood Stabilizers and Breastfeeding

- Transient increases in elevated infant TSH, BUN, Cr
  - Recommendations-consider when
    - Bipolar disorder in mother that is stabile
    - Lithium monotherapy (or is simple regimen)

Mood Stabilizers and Breastfeeding

- Adherence to infant monitoring
  - Monitoring lithium level, TSH, BUN, Cr immediately postpartum, 4-6 weeks of age, and then every 8-12 weeks
- Healthy infant
- Collaborative pediatrician

– Viguera et al., 2007

Medication Issues for Women

- Hyperprolactinemia
  - Antipsychotics: typicals and risperidone, less so with clozapine, olanzapine, quetiapine, and ziprasidone
  - Galactorrhea, irregular menses/amenorrhea, infertility, sexual dysfunction

Medication Issues for Women

- Interactions with oral contraceptives
  - Decreased efficacy of OCs
    - Carbamazepine
    - Oxcarbazepine
    - Topiramate
  - Oral contraceptives may decrease lamotrigine levels

– Sabers et al., 2003

Medication Issues for Women

- Weight gain
  - Not just a women's issue
  - ++++ Clozapine, Valproate
  - +++ Olanzapine, Lithium
  - ++ Quetiapine
  - + Risperidone, Ziprasidone

Medication Issues for Women

- 0 Lamotrigine
- - Topiramate
  - Vanina et al., 2002

Polycystic Ovarian Syndrome (PCOS)

- Association between hyperandrogenism and anovulation
- Endocrine
  - Increased testosterone, luteinizing hormone, low or normal follicle stimulating hormone

Polycystic Ovarian Syndrome (PCOS)

- Clinical
  - Hirsutism, acne, anovulation
- Also
  - Obesity, insulin resistance
- Ovaries have small follicles
  - Not actually cysts

Polycystic Ovarian Syndrome (PCOS)

- Common disorder
  - 4-7% of reproductive aged women

Polycystic Ovarian Syndrome

- Valproate may increase hyperandrogenism, menstrual disturbances
  - First noted in epilepsy literature
- Bipolar disorder
  - Disorder and or medications may be associated with abnormalities in reproductive functions, PCOS
    - Vainonpaa et al., 1999; Isojarvi et al., 1996; Isojarvi 1993

Bipolar Disorder and PCOS

- Bipolar disorder and endocrine abnormalities
  - Women with bipolar disorder were more likely to have early onset menstrual cycle dysfunction compared to women with major depression and healthy controls

Bipolar Disorder and PCOS

- Bipolar disorder: 34.2%
- Unipolar depression: 24.5%
- Healthier controls: 21.7%
- Valproate use may increase risk of PCOS in women with bipolar disorder: small studies

Bipolar Disorder and PCOS

- More menstrual abnormalities, higher androgen levels, higher leptin levels than with lithium
- High rates of menstrual dysfunction with valproate and lithium
  - Joffe at al., 2006; O'Donovan et al., 2002; McIntyer et al., 2003; Rasgon et al., 2000

Perimenopause/Menopause

- Perimenopausal/Menopausal (N=22)
  - 2 women reported onset of bipolar disorder while perimenopausal or postmenopausal disorder
  - N=12 reported worsening of mood
  - N=10 reported no change

Perimenopause/Menopause

- N=0 reported improvement of mood
- Not using HRT associated significantly with report of worsening of mood (P=0.2)
  - Freeman, et al., 2002

Bone Health and Bipolar Disorder

- Mood disorders and schizophrenia have been associated with low bone mineral density (BMD)
- May be due to the disorders and or medications

Bone Health and Bipolar Disorder

- Hyperprolactinemia-associated with bone loss
  - Hyperprolactinemia may cause hypogonadism
  - The presence/duration of low estrogen (and testosterone) appears responsible for bone loss

Bone Health and Bipolar Disorder

- In women with regular menses, hyperprolactinemia not associated with low BMD
- Especially concerning in young women, who require adequate estrogen production for development of adult bone mass
  - Mirsa, et al., 2004

Bone Health and Bipolar Disorder

- Clinical indicators of hyperprolactinemia
  - Galactorrhea
  - Menstrual irregularities
  - Not a risk factor for osteoporosis without hypogonadism

Bone Health and Bipolar Disorder

- Most likely with older antipsychotics, risperidone
  - Misra et al., 2004

Bone Health and Bipolar Disorder

- What should we do?
  - BMD evaluations: DXA (dual energy X-ray absorptiometer)
  - Ask about menstrual cycle (women of reproductive age)
  - Smoking

Bone Health and Bipolar Disorder

- Calcium supplement
  - Bone health (1,000-1,500 mg/day)
  - May have beneficial mood effects (PMS data)
  - But not at same time as a thyroid medication-reduced availability of thyroxine with calcium
    - Singh, et al., 2001

Summary

- Bipolar disorder may be a missed diagnosis
- All mood stabilizers have side effects
- As a group, keep in mind that women of reproductive age may become pregnant on mood stabilizers

Summary

- Keep in mind drug interactions including those with oral contraceptives
- Untreated bipolar disorder has serious consequences

Balancing Risks and Benefits: Cases

- PT is a 28 year old female who was brought into the hospital by friends after telling them that she was considering taking an overdose of pain killers
- She is 6 months pregnant and has recently gone through a difficult separation and divorce

Balancing Risks and Benefits: Cases

- On questioning she is tearful and describes overwhelming feelings of sadness and guilt
- She also states that she has not been sleeping or eating and that she has experienced a 7 pound weight loss over the past four weeks

Balancing Risks and Benefits: Cases

- What antidepressant alternatives are available for PT?

Balancing Risks and Benefits: Cases

- Treatment alternatives
- Tricyclic antidepressants (TCA)
  - Amitriptyline, Imipramine
- Selective Serotonin Reuptake Inhibitors (SSRI)
  - Fluoxetine, Sertraline

Balancing Risks and Benefits: Cases

- Norepinephrine Dopamine Reuptake Inhibitor (NDRI)
  - Bupropion
- Norepinephrine Antagonist/Selective Serotonin Antagonist (NaSSA)
  - Mirtazapine

Balancing Risks and Benefits: Cases

- Serotonin Norepinephrine Reuptake Inhibitors (SNRI)
  - Venlafaxine
- Serotonin Antagonist Reuptake Inhibitor (SARI)
  - Nefazodone, Trazodone

Balancing Risks and Benefits: Cases

- Monoamine Oxidase Inhibitor
  - Phenylzine

Balancing Risks and Benefits: Cases

- What antidepressant and would you recommend for PT?
  - A. Imipramine
  - B. Fluoxetine
  - C. Paroxetine
  - D. Phenylzine

Balancing Risks and Benefits: Cases

- PT is scheduled to deliver her baby in 3 weeks
- She asks if she can breastfeed on her current antidepressant medication
- How do you counsel her?

Balancing Risks and Benefits: Cases

- AY is a 34 year old female who delivered her 5th child 6 weeks ago
- Today she called the police after drowning all of her children in the bathtub

Balancing Risks and Benefits: Cases

- Her psychiatrist recently took her off of haloperidol and citalopram because she wanted to breastfeed her baby
- She has become depressed after the birth of all 5 of her children

Balancing Risks and Benefits: Cases

- How is major depressive disorder with postpartum onset diagnosed?
  - Diagnosis is based on criteria for major depressive disorder
  - Temporal relationship within 4 weeks postpartum

Balancing Risks and Benefits: Cases

- What would have been a more appropriate antidepressant treatment recommendation for AY?
  - A. SSRI
  - B. TCA
  - C. Venlafaxine
  - D. ECT

Balancing Risks and Benefits: Cases

- What would have been a more appropriate antidepressant treatment recommendation for AY?
  - A. SSRI
  - B. TCA
  - C. Venlafaxine
  - D. ECT