**Reproductive Psychiatry: A Lifespan Approach to the Treatment of Women’s Mental Illness**

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**Disclosures**
This presenter will discuss off label use of medication but has nothing else to disclose.

**Objectives**
- Describe gender differences in psychiatric disorders
- Understand psychiatric effects of hormonal fluctuations throughout the lifespan
- Describe most efficacious treatments based on latest evidence

**What are the differences between men and women?**

**How did we find the differences?**
- Structural Imaging
- Gene Mapping

**Functional MRI**

- Increased bilateral locus activity in those with PPD compared with non-PDD women. Right amygdala activity increased during negative emotion task.
- Increased left prefrontal activity in those with PPD compared with non-PDD women. Right amygdala activity increased during negative emotion task.
- In all negative emotion conditions, right PFC activity increased for visualizations.
Structural imaging

Healthy Brain

Depression

Gene Mapping & Pharmacogenomics

- To identify genes or single nucleotide polymorphisms (SNP) that contribute to the etiology and pathogenesis of psychiatric illness
- Tailor treatment to minimize side effects and enhance efficacy

So...What are the differences?

- Differences in psychiatric morbidity and outcome
- Differences in brain structure
- Dramatic fluctuations in reproductive hormones
- Critical periods during female lifespan—higher risk depression.
- SNPs found in women but not in men

Psychiatric Outcomes

Depression

- 1.7 X more likely to report depression from early adolescence to mid 50s. (Kessler et al., 1993)
- ~55 years 2X risk depression as men, but age 55-60 years similar levels of depression as men. (Bebbington et al., 1998)
- Women higher risk for onset depression, and Depressive episodes ~20 weeks longer than men (Eaton et al. 2008)

Gender Differences in Depression

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime prevalence</td>
<td>21.3%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Prevailing symptoms</td>
<td>Atypical (weight gain, increased appetite)</td>
<td>Typical (weight loss, decreased appetite)</td>
</tr>
<tr>
<td>Seasonal onset</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Suicidal tendencies</td>
<td>Attempts</td>
<td>Completed acts</td>
</tr>
<tr>
<td>Areas functional impairment</td>
<td>Marital, family</td>
<td>Work</td>
</tr>
<tr>
<td>Co-morbid disorders</td>
<td>Anxiety, eating disorders</td>
<td>Alcohol, substance abuse</td>
</tr>
<tr>
<td>Help-seeking</td>
<td>More likely</td>
<td>Less likely</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>More migraines, thyroid disease</td>
<td>Less likely</td>
</tr>
</tbody>
</table>

Steiner & Koren, 2003
PTSD
- Pituitary adenylate cyclase activating peptide (PACAP) is a neuropeptide that regulates CRH and found in the limbic system and hypothalamus.
- Found single nucleotide polymorphism PACAP among females
- PACAP blood levels predicted symptoms of PTSD among females only.
- PACAP is estrogen dependent

Reuder et al., (2011)

Anxiety
- Except for OCD and social anxiety, all other anxiety disorders are more common in women
- Galanin (GAL) is a neuropeptide that is induced by estrogen and is estrogen dependent
- It is concentrated in brain regions that regulate mood and anxiety
- A GAL polymorphism on rs948954 causes higher HPA activity and is associated with increased anxiety and vegetative depressive symptoms in females but not males
- Also predicted worse response to antidepressants

Unschuld et al., (2010)

General differences

Females
- Bipolar - rapid cycling, depressive
- Metabolism AD affected by estrogen
- More depression/anxiety
- More eating disorders
- Attention deficit-inattentive
- Borderline

Males
- Bipolar - manic
- Conduct
- Attention deficit-hyperactive
- Substance abuse
- Autistic spectrum
- Narcissistic

Visuospatial Processing
- Males increased activation:
  - Intra-parietal sulcus (numerical cognition)
  - Right lingual and parahippocampal gyri
- Females increased gray matter density:
  - In same areas of brain

Keller & Menon, 2009
Care based vs. Justice Processing

- **Males**
  - Increased activity in superior temporal sulcus (justice area).

- **Females**
  - Increased activity in posterior and anterior cingulate and anterior insula (care-based).

(Harenski et al., 2008)

Lifespan Depression Women

- **Age-specific rate of depression**
  - Increased risk for depression at puberty and then decreases across the lifespan from 25 years regardless of the level of testosterone. (Almeida et al., 2008)

Lifespan Depression Men

Hormonal Fluctuations

Risk for Depression Across the Female Lifecycle

What is so special about estrogen?

- Enhances structure of neurons
- Increases growth factors regulating neuronal growth
- Increases amounts of 5HT, NE, DA
- Enhances glucose metabolism in the brain
- Creates differences in treatment options between younger and older women
Estrogen and Neurons

- Penetrates the neuronal membrane
- Then penetrates the neuronal nucleus
- To reach the estrogen receptors which are near genes (estrogen response elements)


Menstrual cycle & Estrogen

- During the first half of the cycle
  - Estrogen increases
    - Neuronal growth
    - Production of dendritic spines on pyramidal neurons in hippocampus, amygdala, & cortex
    - Production dendritic spines in the hypothalamus
    - Peak of E&P after first half of cycle potentiates dendritic growth


Estrogen & Neurons

- When estrogen binds to its receptor in the cell nucleus of the neuron it regulates gene production of:
  - Brain derived neutrophic factor - plays role in neurogenesis
  - Neurotransmitter synthesizing enzymes
  - Neurotransmitter metabolizing enzymes


Menstrual Cycle & Estrogen

- Second half of the cycle, when Estrogen Falls & Progesterone increases
  - Down-regulation of dendritic spines which may be a mechanism for PMDD
  - Decrease # synapses


Estrogen receptors

- Highest concentrations:
  - Hippocampus - influences mood & memory
  - Cerebral cortex- influences mood & cognition
  - Amygdala -influences anxiety & cognition
- Therefore reduced estrogen can contribute to symptoms of MDD such as:
  - Decreased concentration
  - Lowered mood
  - Increased anxiety


GABA, Glutamate & Estrogen

- Estrogen inhibits GABA
  - Activation pyramidal neurons
  - Release glutamate
  - Activation NMDA receptors on post synaptic neuron
  - Increased dendritic spine formation.
- When estrogen falls in the second half of the cycle this process is reversed.

Estrogen & Serotonin

- Increases 5HT by preventing 5HT1a receptor auto-inhibition
- Increasing 5HT2a receptors in prefrontal cortex--> improved cognition

(Kugaya, Epperson, & Zoghbi (2003))

Estrogen & Brain Glucose

- Increases expression of glucose transporters at the BBB on the membranes of neurons
- Allows higher brain energy by increasing glucose access
- Low estrogen signals hypothalamus to increase brain blood flow to increase brain glucose levels.

Estrogen & Norepinephrine

- Increases norepinephrine by increasing mRNA for tyrosine hydroxylase (key enzyme to produce NE).
- Increases norepinephrine in hypothalamus via alpha 1 receptors which regulate appetite, libido, and sleep.

Other Trimonoamine Modulators

- Thyroid hormone
- Lithium
- L-methylfolate
- Brain stimulation
- Psychotherapy

Estrogen & Dopamine

- Prevents reuptake of DA at the DA transporter--> increased interest and pleasure

Pharmacotherapy

- SSRI during pregnancy?
- SSRI during breastfeeding?
- ERT or OCS?
- During adolescence?
Adolescence

- After birth, we have the most number of neurons by age 6
- But in adolescence, there is a normal process of competitive pruning
- We lose 1/3 to ½ our neurons
- See onset psychiatric disorders because unmasked

Pharmacokinetics in Women

- Higher percentage body fat
- Higher cerebral blood flow
- Slower gastric emptying time
- Decreased gastric acid secretion
- Lower body weight
- Less blood volume
- Lower plasma protein binding
- Lower hepatic biotransformation
- Slower renal clearance

Neurodevelopment

- Synaptogenesis
- Differentiation & Myelination
- Migration
- Neuronal Selection
- Neurogenesis

Women & Antidepressant pharmacokinetics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine/desipramine</td>
<td>Higher drug plasma concentrations in women &lt;50 years</td>
</tr>
<tr>
<td>Amitriptyline/nortriptyline</td>
<td>Higher drug plasma concentrations in women &lt;50 years</td>
</tr>
<tr>
<td>Clomiprime</td>
<td>Longer half-life and clearance</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Higher drug plasma concentrations at 200mg/dl vs. 100mg/dl</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Higher drug plasma concentrations</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Longer half-life</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Higher Vd</td>
</tr>
<tr>
<td>Venlafaxine/Buproprion</td>
<td>No differences</td>
</tr>
</tbody>
</table>

Hormonal effects on pharmacokinetics antidepressants

- OCPs
  - Increased metabolism in AD with conjugation/glucoronidation
  - Decreased clearance in AD with oxidation
  - May need to adjust does of AD in reduce if decreased clearance
- Menstrual cycle
  - Possible decreased steady state during luteal phase as much as 5%
- Pregnancy
  - Changes in gastric motility, volume distribution, protein binding, hepatic metabolism may need increased dosage.
Treatment Adolescent Females

- Caution with SSRIs in adolescents because of increased risk suicidality < 25 years.
- First line psychotherapy unless severe depression.
- Fluoxetine is the only AD with documented efficacy with FDA approval.

PMDD treatment

- Anti-anxiety agents may be helpful (alprazolam, buspirone)
- Can treat during luteal phase (2 weeks prior to menses)
- GnRH agonists – suppress ovulation → decr FSH, LH
  - Bromocriptine, Danazol (possible hirsutism, breast pain, nausea), Leuprolide, Goserilin, Buserilin
- NSAIDs, diuretics
- Agents that increase DA and NE not helpful
- Reduce refined sugar, artificial sweeteners, caffeine
- Frequent snacks, complex carbohydrates

PMDD

- Irritability, depressed mood, anxiety, mood swings late luteal phase
- May be unmasking underlying depression through menstrual magnification
- Increased risk onset MDD

PMDD - treatment

- Nutritional supplements: Vitamin B6, carbohydrate rich beverages, magnesium, vitamin E, calcium
- Psychotherapy (CBT, IPT)
- Aerobic exercise, relaxation, yoga, meditation
- Medications
  - SSRIs/fluoxetine, sertraline, Paroxetine, citalopram – can give luteal phase
  - TCA (clomipramine)
  - Yasmin (low dose E&P)
  - SNRI
    - DA and NE not helpful

Pregnancy

Risks Treatment
- Cardiac anomalies (1st trimester especially paroxetine)
- NTD (1st trimester)
- PPHN (3rd trimester)
- Neonatal withdrawal (1st trimester)
- Prematurity, LBW
- LT dev. Abnormalities
- Increased suicidality <25 yrs

Risks No Treatment
- Poor prenatal care
- Poor mother-infant bonding
- LBW
- Developmental delay
- Harm, neglect infant
- Relapse MDD
- Increased suicidality
- Poor self-care
- 68% relapse vs. 25% when D/C AD

Postpartum

- Estrogen levels plummet after childbirth
- 90% psychiatric episodes within 4 weeks postpartum
- 63% risk recurrence untreated vs. 6%
- Emotional, cognitive, behavioral problems in children through adulthood
- Marital & family dysfunction
- Poor self-care
- Infant safety
- Self-harm
- Treatment resistant/chronic depression

Posmontier
Perinatal impact

<table>
<thead>
<tr>
<th>Illness</th>
<th>OB</th>
<th>Neonatal</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Forceps, prolonged labor; PTL, Sp Ab</td>
<td>Developmental delay</td>
<td>BZ, AD, psychotherapy</td>
</tr>
<tr>
<td>Major Depression</td>
<td>LBW, IUGR</td>
<td>Increased cortisol, catecholamines, crying, NICU admissions</td>
<td>AD, Psychotherapy, ECT</td>
</tr>
<tr>
<td>Bipolar illness</td>
<td>Same as MDD</td>
<td>Same as MDD</td>
<td>Lithium, antipsychotics, anticonvulsants, ECT</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>PTL, LBW, SGA, abnormal placenta, antenatal hemorrhage</td>
<td>Increased death</td>
<td>Antipsychotics</td>
</tr>
</tbody>
</table>

ACOG Practice Bulletin #92, 2008

Medication Considerations

<table>
<thead>
<tr>
<th>Medications</th>
<th>Category</th>
<th>Benefits</th>
<th>Risks</th>
<th>Lactation</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZ</td>
<td>D, X</td>
<td>Unknown of concern</td>
<td>L3, L4</td>
<td>Quasapram (Dural)</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>B, C</td>
<td>Unknown of concern</td>
<td>L3</td>
<td>Sonata 2, L4</td>
<td></td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>B, C</td>
<td>Unknown of concern</td>
<td>L3</td>
<td>Lithium, AAP contraindicated, L4</td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>C</td>
<td>Unknown of concern</td>
<td>L1, L2</td>
<td>Esiprin L5</td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>C</td>
<td>Unknown of concern</td>
<td>L2</td>
<td>Lamivudine D, Lexapro older infants, L3, Prozac, escitalopram L3</td>
<td></td>
</tr>
<tr>
<td>Other AD</td>
<td>C</td>
<td>Unknown of concern</td>
<td>L3</td>
<td>Lamivudine L3, Vaxdine L4</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>C</td>
<td>Unknown of concern</td>
<td>L3, L4</td>
<td>Clozapine, Haloperidol L3</td>
<td></td>
</tr>
</tbody>
</table>

Pregnancy

- Consider gestation age before treatment
- Weigh risks and benefits of medications
- May need higher doses since increased clearance in second half of pregnancy
- Single med at higher dose better than multi-meds
- Choose med with lower metabolites, higher protein binding, fewer interactions with other meds.
- Consider psychotherapy if mild illness
- Consult Reprotox (www.reprotox.org), TERIS (http://dpts.washington.edu/terisweb)

Pregnancy Safety Medications

- Category A
- Category B
- Category C
- Category D
- Category X

- L1: Safer
- L2: Moderately Safer
- L3: Possibly Hazardous
- L4: Contraindicated

Postpartum

- Medications can pass into breastmilk so check lactation ratings
- May need to decide to continue breastfeeding if severe disease
- Check thyroid function
- Can't use estrogen because of hypercoagulability
- Psychotherapy
Perimenopause/Menopause
- Age 47 cycles change/skipped, ~age 51 stops
- VM symptoms late perimenopause, early menopause
  - Perimenopause- estrogen fluctuations (5-7 yrs)
  - Menopause – Brain blood glucose fluctuations
- 4 X increased risk depression with VM symptoms
- Increased risk depression with history
- Even if no depression history, twice as likely to experience new onset MDD

Symptoms
- Vasomotor – hot flashes, night sweats, palpitations
- Affective: depressed mood, anxiety, mood swings
- Cognitive: poor memory and concentration, forgetfulness
- Somatic: dizziness, fatigue, headache, insomnia, joint pain, paresthesias
- Physical: urogenital atrophy, dyspareunia, osteoporosis, cardiovascular disease

Labs
- Perimenopause
  - Estradiol < 40 pg/ml
  - FSH > 25 IU/L
- Menopause
  - Estradiol < 25 pg/ml
  - FSH > 40 IU/L

Overlap VM & Depression
- Depression
  - Low energy
  - Depressed Mood
  - Anhedonia
  - Agitation/retardation
  - Suicidal ideation
- Perimenopause/Menopause
  - Hot flashes
  - Sweating
  - Vaginal dryness

VM Symptoms & Depression
- Regulated by DA, 5HT, NE
- VM through hypothalamus thermoregulation
- Depression through VMFPC, amygdala, brain stem, hypothalamus
- Fluctuating estrogen levels can disrupt can dysregulate monoamines → VM in perimenopause
- Low levels brain glucose transporters can → VM in postmenopausal women
  - b/c hypothalamus responds by increasing brain blood flow
  - Increased brain glucose
  - May be exacerbated by DM
VM Symptoms & Depression

- In the hypothalamus (monkey studies)
  - 5HT increases core body temperature
  - NE decreases core body temperature

- Treating VM symptoms could decrease depressive symptoms

- Treating VM symptoms could prevent MDD relapse and sustain remission

Other therapies to consider

- Micronutrients
  - Vitamins B, D, E, Carnitine, Inositol, Magnesium, Selenium, Zinc
  - Omega 3 fatty acids
  - Exercise
  - Yoga, meditation, massage, music
  - Light therapy

Treatment

Perimenopause

- High dose transdermal estrogen (100µg/day vs. 5µg/day) effective but associated health risks.
- SSRI effective < 44 years b/c works better in presence of estrogen
- Psychotherapy

Menopause

- High dose transdermal estrogen patch not effective
- SSRI not effective > 44 years and has no effect on VM symptoms
- SNRI
- Psychotherapy

SNRI effective across lifespan for VM symptoms and depression regardless of estrogen levels

Perimenopausal Case Study

- 50 year old woman
  - sweats and hot flashes (6-7 episodes/day)
  - Difficulty falling asleep
  - Emotional liability, and crying outbursts - worse in winter months
  - Feels anxious and guilty
  - No suicidal thoughts
  - Lost her sexual drive, with some dryness and low libido.
  - Irregular periods over the last year, lighter menstrual flow
  - Medical - mild to moderate arthritis lumbar spine, neck.
  - No previous psychiatric history
  - Family history non-contributory
  - Social: Occasional glass wine, non-smoker, no illicits, lives with husband, 2 teenage children, employed full-time as RN

Management Suggestions

- Labs: FSH, Estrogen, Thyroid, CBC, Chem profile, UA, Vitamin D levels, micronutrients
- CBT, IPT, other
- SNRI-desvenlafaxine (indicated for pain also)
- Ambien prn
- L-methyfolate, vitamin D prn, calcium intake, micronutrient supplementation prn
- Dietary: omega 3
- Light therapy
- Exercise, yoga, relaxation, meditation
- OTC vaginal lubricant prn

One more thing....

L-Methyfolate

- Can cross BBB unlike folic acid
- Needed to produce BH4 (co-factor for tryptophan and tyrosine hydroxylases)
- BH4 is critical in formation monoamines.
- Especially important if taking anticonvulsant mood stabilizer (decreases folate)
Conclusions

- Women are more vulnerable to depression because of fluctuating estrogen levels
- Estrogen affects levels of DA, 5HT, NE, brain glucose, vasomotor symptoms
- Tailor treatment to the lifecycle stage
- SSRI beneficial for pre-menopausal women
- SNRIs best for post-menopausal women
- Don’t forget about L-Methylfolate
- Consider risks in adolescence, pregnancy, and breastfeeding.