Women, ovarian hormones, and relapse to addiction

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Special thanks to Louann Brizendine, MD for use of some of her slides
General Overview

- Neuroscience of addiction
- Women and hormone fluctuations
- Women and relapse to addiction: how hormones may play a role
  - Relapse in women and ovarian hormones
  - Mood, stress, and relapse in women
  - Relapse risk across menstrual cycle
  - Postpartum
  - Perimenopause
- Treatment implications
Stages of Addiction

• Acute drug effects
  – Drug used intermittently for rewarding effects

• Transition to Addiction
  – Behavior looks like addiction
  – Neuron changes return to baseline after drug discontinuation

• End Stage Addiction
  – Drug use to relieve craving, loss of control of drug use
  – Long standing changes in neuron function
Relapse Triggers: Insight from Animal Studies

- Re-exposure to small amount of drug
- Re-exposure to an environment associated with drug use
- Re-exposure to cues associated with drug use
- Emotional distress or exposure to stressful events
Deciding to Use: Relapse

- Exposure to trigger
- Associate cue with past reward
- Determine how much the drug is wanted
- Choice to use drug
- Action to procure and ingest drug
Role of Dopamine

- Released in response to novel stimuli and promotes learning
- Released by drugs of abuse, reinforcing drug seeking behavior
- In addict, released in response to environmental stimuli associated with past drug use, turning on pre-existing brain circuits, triggering well-learned drug-seeking behavior
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Menstrual Cycle

Sex steroid changes in human menstrual cycle.
Postpartum, Pregnancy and Menstrual Hormone Levels

![Graph showing hormone levels during menstrual and pregnancy phases.](image)
Fertile Perimenopause Menopause

Estrogen and Progesterone in the Female Lifecycle

Erratic estrogen

Erratic FSH
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Women vs. Men

- Women have *greater craving* compared to men in response to nicotine and cocaine drug cues.
- Women are *more likely to relapse* to cigarette use during and after treatment, and have shorter abstinence periods after cocaine treatment. However they have a better prognosis than men six months after residential cocaine treatment.
- Women *progress to addiction more rapidly* than men (‘telescoping’).
- However, there is a *lower prevalence* of stimulant and alcohol use disorders in women compared to men.
- Women have a *lower subjective high* in response to stimulants compared to men.
Relapse and addiction in women

- Some studies show women have greater dopamine release in the brain in response to stimulant administration compared to men (Riccardi, 2006).
- Others show that women have lower dopamine release in response to stimulant administration (Munro et al., 2006).
## Hormonal Influence on Addictive Behavior: Preclinical Data

<table>
<thead>
<tr>
<th></th>
<th>Neurobiological effect</th>
<th>Behavioral effect</th>
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</thead>
<tbody>
<tr>
<td><strong>Estrogen</strong></td>
<td>Enhances the effect of dopamine</td>
<td>Increases reward, development of addiction, and relapse/reinstatement</td>
</tr>
<tr>
<td><strong>Progesterone</strong></td>
<td>Variable effects on dopamine</td>
<td>Decreases response to stress, anxiety, and aggressiveness</td>
</tr>
<tr>
<td><strong>Allopregnenolone</strong></td>
<td>Enhances GABA-A (similar to alcohol and valium)</td>
<td>Reinforcing, triggers relapse/reinstatement to alcohol use at low doses, at high doses decreases alcohol intake</td>
</tr>
</tbody>
</table>
Dopamine Pathways and Estrogen
Bringing it all together

- Progesterone/allopregnanolone may blunt dopamine (or other neurotransmitter?) release by stimulants, and decrease subjective high.
- Estrogen may increase dopamine release, speeding up the process of developing drug dependence, and exacerbating craving.
- How these hormones play a role in the differences in relapse behavior between women and men still needs to be clarified.
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Mood, Stress, and Relapse in Women

- Women report *higher levels of craving and depressed mood* during abstinence from cigarettes.
- Women experience *stronger urges* to smoke and drink *when depressed*.
- Women are more likely to report substance use *relapse in response to stressful events or depressed mood*.
- Women have *heightened physiologic response to social stressors*, and increased HPA responsiveness is associated with increased risk of cocaine relapse.
What happens to mood during times of hormone fluctuation?

- **Menstrual cycle changes:** PMDD (which is not necessarily seen with PMS) / Premenstrual exacerbation. The female brain experiences hormonally determined emotional fluctuations. Not a big deal for 80%. A VERY big deal for 8-10%.

- **Postpartum:** 10% women have postpartum depression.

- **Perimenopause:** Crying easily, mood swings, sleep problem, fatigue, irritability and weight gain, sexual complaints. 1st depression ever for 54% of the perimenopausal women who get depressed.
Mood Changes Across the Menstrual Cycle

Best

Worst

week

1  2  3  4

Morales, 1986
Menstrual Cycle Week and All Psychiatric Admissions

- If random, admissions of women to psychiatric hospitals for all psychiatric diagnoses would be 25% on each week of the menstrual cycle.
Psychiatric Admissions in 2 Years Before and After Delivery

*Rate of psychiatric admissions in the 2 years before and after delivery in a population of 470,000 people with 54,087 births in a 12-year period
How do hormones play a role in these mood changes?

- Estrogen: increases neuronal excitability, stimulant effect.
- Progesterone/allopregnanolone: inhibitory effect, sedating.
- Fluctuations cause unstable mood.
- Crashing allopregnenolone during the late luteal phase may increase anxiety due to withdrawal.
- Estrogen and progesterone affect expression of the serotonin transporter, which is implicated in depression.
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Hormones, relapse, and menstrual cycle: theories

- Estrogen helps dopamine activity, may increase relapse risk and craving during follicular phase.
- Progesterone/allopregnanolone withdrawal during the late luteal phase may trigger anxiety/dysphoria and thereby increase relapse risk and craving.
- Low physiologic reactivity to psychosocial stress during first two weeks of the menstrual cycle compared to the third and fourth weeks may decrease vulnerability to relapse during the first two weeks.
Relapse across menstrual cycle

- Nicotine withdrawal symptoms (in some studies) increase during the luteal phase.
- Increased alcohol intake during the luteal phase. One study only.
- No studies of cocaine craving and withdrawal across menstrual cycle.
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Relapse postpartum

- 45% of women who intended to maintain abstinence, when polled while pregnant, resumed (Roske et al. 2006).
- Whether relapse is related at all to hormonal shifts is difficult to determine.
- Delay discounting predicts relapse to cigarette smoking post partum (Yoon et al. 2007).
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Relapse in Perimenopause

- No studies of perimenopause.
- One study of HRT in post menopausal women showed no effect on smoking cessation and an increase in depressive symptoms on HRT (Allen, 2003).
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Treatment implications

- **Track** craving and mood symptoms in relation to the patient’s menstrual cycle
- **Educate** about triggers for relapse and to be especially vigilant during vulnerable times
- **Provide** psychotherapy to bolster coping strategies for stressful life events
- **Screen** for comorbid mood or psychiatric disorders and refer for treatment; consider pharmacotherapy for relapse prevention
- **Refer** for treatment of premenstrual mood symptoms with a selective serotonin reuptake inhibitor and/or hormone regulation
Affective Disorders in Women

Risk for Depression by Age & Sex

Importance of support: psychotherapy, 12 step

- Women respond more to verbal coping strategies.
- In a 6-month follow-up outpatient study of cocaine dependence, women responded better than men did to behavioral treatment, even though the women had more-severe disorders at entry.
Pharmacotherapy: Relapse Prevention

- Decrease reward value/ reinforcing effects of drug
  - methadone, nicotine replacement
- Weaken conditioned memories
  - acamprosate, topiramate
- Increase worth and enjoyment of non-drug reinforcers
  - bupropion
- Decrease stress response
  - CRF antagonists (not approved)
- Interfere with withdrawal
  - clonidine

(Baler and Volkow, 2006)
Pharmacotherapy: Relapse Prevention in Dual Diagnosis

- Bupropion treats depressive symptoms and nicotine dependence in smokers. In women more than men, aids recovery from lapse during smoking cessation treatment.
- SSRIs treat MDD and alcohol dependence in patients with both diagnoses.
- Buspirone decreases return to heavy drinking and decreases anxiety in alcoholics with GAD.
- Lamotrigine and memantine decrease depressed mood during alcohol withdrawal.

(Wilyeto et al. 2007) (Brady and Verduin, 2005)
Oral Contraceptives (OCPs)

- Studies of relapse with continuous OCP hormone control are needed before we would recommend this treatment routinely.
- For individual women who report mood changes and craving during periods of hormonal fluctuation: consider referral for a trial of continuous OCPs to stabilize hormone levels in the late luteal phase (Sesonale, Necon 0.5/35 or 1.0/35).
Risk factors for a negative response to OCPs

- history of depression or other psychological distress symptoms
- dysmenorrhea
- PMS
- history of pregnancy-related mood symptoms
- family history of OCP-related mood complaints
- being in the postpartum
- age <30
Risk of taking Oral Contraceptive Pills

• Patient should enquire from PCP or psychiatrist about risks.
• Because of the increased risk of clotting, only nonsmokers and women without a history of blood clots should take OCPs.
• Women with breast cancer or endometrial cancer should not take OCPs.
### Response to Estrogen in Depressed Perimenopausal Women

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Authors</th>
<th>Participants</th>
<th>Response Rate</th>
<th>Placebo Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Soares et al</td>
<td>50 women</td>
<td>68% full or partial response</td>
<td>20%</td>
</tr>
<tr>
<td>2000</td>
<td>Schmidt et al</td>
<td>34 women</td>
<td>80% full or partial response</td>
<td>22%</td>
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</tbody>
</table>
Example Case

- Ms. H, age 46, is in her third month of an alcohol and drug residential rehabilitation program. She has a 10-year history of alcohol and crack cocaine dependence and is battling cravings to use again. These feelings are usually triggered by being in places or with people associated with her drug use, but this time she is committed to staying sober. She started smoking cigarettes in her teens and using drugs and alcohol in her mid 20s. She feels that her dependency has been out of control in the 10 years since her son was born. She has tried to quit many times on her own but has managed no more than 1 month of abstinence. She often has relapsed in response to feeling anxious or depressed about being unemployed or after arguing with her partner.
What do you want to ask her?

• Regular menstrual periods and changes in frequency lately?
• Changes in mood during menstrual periods and especially just before her period?
• Have you ever tried medications or therapy?
Example Case

- Ms. H. reports increased irritability and impulsivity along with depressed mood—especially during the 3 to 4 days preceding her menstrual period. Her periods are regular, and these mood symptoms recur each month. She does not meet criteria for major depressive disorder. Eight months ago, when Ms. H was still using cocaine, her primary care physician prescribed fluoxetine, 20 mg/d, for depressive symptoms. Her mood has not improved, nor has her menstrual cycle-related depression or irritability. She asks if anything else might stop her premenstrual cravings.
What might you suggest?

• Have patient track mood changes and cravings across month, and educate about possible risk of premenstrual and perimenopausal periods of time.

• Refer for psychiatric evaluation and possible treatment with hormone replacement therapy/OCPs, or medications like acamprosate, topiramate, or buproprion.

• Refer for psychotherapy addressing interpersonal skills and coping with other life stressors and encourage 12 step attendance.
Take home points

- Ovarian hormones may influence relapse behavior.
- Understanding neurobiology helps us counsel our patients about their risk of relapse.
- Women are especially vulnerable to stress, mood, and craving.
- Treatment should focus on these vulnerabilities.
Thanks for your attention!

For any more information or references on the subject, please feel free to access the article from Current Psychiatry: