

For women only: Hormones may prevent addiction relapse

Stabilizing monthly cycles can help some patients



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Women become dependent more rapidly than men after initial cocaine, opioid, or alcohol use and may be more sensitive to drugs' adverse health effects.¹ And although men and women relapse to substance use at similar rates, ovulating women may be particularly vulnerable to relapse at certain times of the month.

Understanding the hormonal influences that increase women's relapse risk can help you intervene more effectively. This article describes:

- how women's relapse patterns differ from men's
- why psychotherapy and hormone regulation may be preferred for relapse prevention in women with substance use disorders.

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CASE REPORT: WILL SHE RELAPSE AGAIN?

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.

MECHANISMS OF RELAPSE

Dopamine release is essential for encoding learned associations. When a drug is used in the early dependency state, dopamine release produces pleasure that reinforces continued drug use. Once the behavior is learned, environmental stimuli can trigger dopamine and turn on the brain circuits for this familiar, highly rewarding behavior. Dopamine also is the primary cause of long-lasting brain changes that make it difficult for substance-dependent persons such as Ms. H to control desire for the drug.²

Early relapse—caused by dopamine's and other neurotransmitters' effects on various brain regions—is triggered by environmental stimuli such as:

- re-exposure to a small amount of the drug
- exposure to an environment or cues associated with past drug use
- exposure to stressful events.

These effects lead from craving to increased

likelihood to engage in behaviors to procure the drug and ultimately to relapse (*Table 1, page 42*).²⁻⁴

EMOTIONS, STRESS TRIGGER RELAPSE

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.

Emotional reactions play a larger role in relapse for women than for men. Women report higher levels of craving and depressed mood during abstinence and experience stronger urges to drink and smoke when depressed. Women also are more likely to report substance use relapse in response

to specific stressful events, disappointments, or depressed mood.¹ This is consistent with evidence that women have heightened physiologic responses to social rejection and social stressors.⁵

A lower density of brain serotonin transporter has been associated with a higher risk of depression in women.

Because estrogen and progesterone affect expression of the serotonin transporter, changes in these hormone levels might alter the risk of depression.⁶ Thus, ovarian hormones' effect on the serotonin system may contribute to the higher rate of emotionally triggered relapse in women versus men.

Menstrual cycle phases. How men and women respond to stress may contribute to differences in their relapse behaviors (*Table 2, page 45*).

During the first 2 weeks of the menstrual cycle—the follicular phase—women show lower physiologic reactivity (as seen in blood pressure and catecholamine measurements) and lower cortisol responsiveness than men do in response to psychosocial stress. Estrogen con-

Compared with men, women experience stronger urges to drink and smoke when depressed

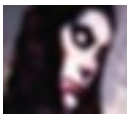


Table 1

3 stages of relapse and their neurobiologic components

| Relapse stage | Key neurotransmitters | Brain regions involved |
|--|--|---|
| Early relapse triggered by: <ul style="list-style-type: none">• exposure to a small amount of the drug• environmental cues that re-trigger learned associations• stressful events and disappointments | Dopamine Dopamine Norepinephrine, corticotropin-releasing factor | Ventral tegmental area Nucleus accumbens core Prefrontal cortex Basolateral amygdala Nucleus accumbens core Extended amygdala Bed nucleus of the stria terminalis |
| Craving | Multiple, undetermined | Prefrontal cortex circuitry involving the anterior cingulate and orbitofrontal cortices |
| Relapse | Glutamate, dopamine | Prefrontal cortex Nucleus accumbens core Ventral pallidum |

Source: References 2-4

tributes to this effect by attenuating sympatho-adrenal responsiveness.⁵

During the latter 2 weeks of the menstrual cycle—the luteal phase—the ovulating woman’s hypothalamic-pituitary-adrenal (HPA) axis response increases and increases her sensitivity to stress. In this phase, progesterone’s presence reverses estrogen’s effect and makes the brain more reactive to emotions and stressors.

Higher stress responsiveness is associated with increased cocaine craving.^{7,8} A 20-year literature review of the role of substance abuse in depression indicates that HPA axis responsiveness of depressed women exceeds that of depressed men.⁹

Summary. Women may be more susceptible than men to emotionally triggered relapse, especially during the menstrual cycle’s luteal phase. Women

may also be more susceptible than men to relapse in response to nicotine and cocaine cues.

MENSTRUATION AND RELAPSE PATTERNS

Research into a correlation between menstrual cycle phases and dependency behavior is in its infancy. Early nicotine, alcohol, and stimulant addiction studies have shown inconsistent results. **Nicotine.** A naturalistic study of women smokers ages 20 to 39 showed that they smoked more cigarettes per day during the late luteal phase, but their nicotine boost and mood states were similar throughout the menstrual cycle.¹⁰

Some—but not all—studies suggest that nicotine withdrawal symptoms increase during the luteal phase.^{11,12} In an outpatient study designed to assess hormonal effects on nicotine response, 30 female smokers acutely abstinent of

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nicotine were randomly assigned by menstrual cycle phase to receive transdermal nicotine or a placebo patch. Both premenstrual and nicotine withdrawal symptoms intensified in the women's late luteal phase, compared with the follicular phase.¹²

Conversely, the same researchers found that menstrual cycle phase did not affect withdrawal symptoms in 21 nicotine-dependent female inpatients, even though premenstrual changes occurred in the late luteal phase.

As the authors observed, drawing conclusions can be difficult when menstrual cycle hormone withdrawal and nicotine withdrawal symptoms overlap.¹²⁻¹⁶

Alcohol. Premenstrual syndrome (PMS) increases a woman's risk of alcohol abuse. Alcohol and allopregnenolone—progesterone's neuroactive metabolite—both facilitate gamma-aminobutyric acid ionotropic type A (GABAA) receptor activity. Thus, women with PMS and alcohol dependence may have a genetically more-sensitive GABAA system.¹⁷ Unfortunately, aside from one study that shows increased alcohol intake during the luteal phase, no studies have examined alcohol withdrawal, craving, and relapse across the menstrual cycle.¹⁸

Stimulants. Stimulant craving and relapse have not been examined in women at different menstrual cycle phases. Some authors speculate that women may have a higher subjective response to stimulants during the early follicular phase—when estrogen levels are higher and progesterone levels are lower—compared with the luteal phase.¹⁹

SEX HORMONES AND RELAPSE

Estrogen. Preclinical studies suggest that estrogen facilitates substance dependence by enhancing dopaminergic activity (*Table 3, page 46*).^{1,20-26} Because reinstatement (the animal model of relapse) is driven partially by dopaminergic activity in the striatum, one could hypothesize that:

Table 2

Substance use relapse patterns: Women versus men

Emotions and mood state play a greater role in driving relapse in women

Craving. Women have greater craving than men in response to nicotine and cocaine drug cues

Nicotine dependency. Women are more likely to relapse to cigarette use

Abstinence. Women have shorter abstinence periods after cocaine treatment

Residential treatment. Women have a better prognosis than men 6 months after residential cocaine treatment

Premenstrual hormone changes increase women's relapse risk

- estrogen's dopamine-enhancing effects facilitate dependence
- women with stimulant dependence are at higher risk of relapse in the follicular phase—when estrogen levels are higher—than in the luteal phase.

Progesterone. Progesterone's effect on dopamine release is unclear. In humans, allopregnenolone may curb relapse during the height of the luteal phase but cause anxiety when its levels drop. Thus, allopregnenolone withdrawal may promote craving and relapse late in the luteal phase.¹⁷ Allopregnenolone's possible effect on relapse has not been confirmed in human studies, however.

TREATMENT IMPLICATIONS

Psychotherapy. Evidence suggests that emotions and mood states may play a larger role in triggering substance abuse relapse in women than in men. Psychotherapy and residential treatment

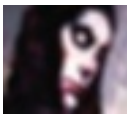


Table 3

Preclinical findings: How hormones may influence addictive behavior

| Hormone | Neurobiologic effect | Mechanism | Behavioral effect |
|-------------------------------------|--|---|--|
| Estrogen | Facilitates dopamine | Decreases inhibitory GABAB activity, regulates D2 autoreceptor expression, alters dopamine reuptake, modulates glutamate activity | Enhances reward, self-administration, sensitization,* and stimulant dependence; facilitates reinstatement [†] |
| Progesterone | Facilitates dopamine when given intermittently; might facilitate or inhibit estrogen's effects on dopamine | Unclear | Attenuates response to stress, anxiety, pain, aggressiveness |
| Allopregnenolone[‡] | Facilitates GABAA | GABAA-positive allosteric modulator, such as ethanol | Enhances ethanol consumption, promotes ethanol reinstatement |

GABAA/GABAB: gamma-aminobutyric acid, ionotropic types A and B

* Sensitization: Repeated exposure to psychostimulants results in drug-seeking response to subsequent exposure, which plays an important role in addiction and craving.

[†] Reinstatement is the animal model of relapse.

[‡] Progesterone's neuroactive metabolite

Source: References 1, 20-26

therefore are particularly important components of women's treatment.

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.^{27,28}

A more-recent inpatient study followed 64 men and 37 women hospitalized for treatment of cocaine dependence. Researchers compared the patients' drug use histories, psychiatric diagnoses, and Addiction Severity Index (ASI) scores during hospitalization and their cocaine use and ASI scores 6 months later. In initial evaluations, women had significantly more-severe family and social problems. At follow-up, however, significantly more women than men were abstinent

from cocaine use, and their family/social problems had diminished.²⁸

Notably, a recent functional MRI study comparing 17 male and 10 female abstinent cocaine-dependent subjects indicated that the women more often used verbal coping strategies to decrease cocaine craving.²⁹ This finding supports the potential benefit of psychotherapy to prevent relapse in women with a history of substance dependence.

Hormone regulation. For many women, continuous oral contraceptives (OCPs) can improve affect variability across the menstrual cycle and diminish negative mood. Others, however, experience negative changes in mood or affect while taking OCPs. Risk factors for a negative response include:

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- 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 <20 years.³⁰

Careful studies of relapse with continuous OCP hormone control are needed before we would recommend this treatment routinely. For individual women at risk for relapse, however, you might consider using continuous OCPs to stabilize hormone fluctuations in the late luteal phase.

Continuous OCPs can be given so that women have only two to three menstrual periods per year. Formulations with ethinyl estradiol and norethindrone—such as Necon 0.5/35 or 1.0/35—may stabilize mood more effectively than others.

Give a 2-month trial, then re-evaluate progress. Because of the increased risk of clotting, only nonsmokers and women without a history of blood clots should take OCPs.

CASE REPORT: FIGHTING THE CRAVINGS

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.

Because of Ms. H's reported PMS, we counsel her to be especially vigilant for alcohol cravings around the luteal and late luteal phases of her menstrual cycle (*Table 4*). We discuss with her:

- the need to watch for signs of relapse
- the importance of aggressive treatment, including psychotherapy, group therapy, and residential treatment, as needed.

Table 4

Interventions to prevent relapse in women with addiction disorders

Track craving and mood symptoms in relation to the patient's menstrual cycle

Educate her about triggers for relapse

Provide psychotherapy to bolster her coping strategies for stressful life events

Screen for comorbid mood or psychiatric disorders and treat them aggressively

Treat premenstrual mood symptoms with a selective serotonin reuptake inhibitor and/or by regulating hormone levels with a continuous oral contraceptive

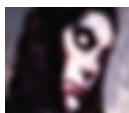
We continue fluoxetine, which has decreased alcohol consumption in some studies.³¹ In collaboration with her primary care physician, we also prescribe an oral contraceptive for Ms. H to take continuously to stabilize her mood across the menstrual cycle.

She agrees to a 2-month trial, and we schedule a follow-up appointment to re-evaluate her progress.

Ovulating women are especially vulnerable to substance abuse relapse during certain menstrual cycle phases. Treat premenstrual symptoms with selective serotonin reuptake inhibitors, and/or regulate mood fluctuations with continuous oral contraceptives in selected patients. For women who relapse, early residential treatment appears most effective.

BottomLine

continued



Related resources

- ▶ Carroll ME, Lynch WJ, Roth ME, et al. Sex and estrogen influence drug abuse. *Trends Pharmacol Sci* 2004;25(5):273-9.
- ▶ Roth ME, Cosgrove KP, Carroll ME. Sex differences in the vulnerability to drug abuse: a review of preclinical studies. *Neurosci Biobehav Rev* 2004;28(6):533-46.
- ▶ Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005;8(11):1481-9.

DRUG BRAND NAMES

Fluoxetine • Prozac
Ethinyl estradiol and norethindrone oral contraceptive • Necon, others

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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