Sex Differences in Depressed Substance Abusers

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Objective: The main goal of this article is to highlight gender-specific differences in the epidemiology, clinical nature, and treatment responses of comorbid depression and substance abuse. The second goal is to make recommendations for future research in the area of gender-specific aspects of comorbid depression and substance abuse.

Data Synthesis: A literature review was conducted using the keywords *sex*, *gender*, *depression*, and *substance use disorders* for the time period 1980 to the present. We first outline the well-known sex differences in the epidemiology of depressed substance abusers and discuss the clinical significance of substance abuse in depression. Two distinct ways of understanding the role of substance abuse in depression are presented. The first is the role that depression may play in escalation of substance use, and the second is depression as a common sequela of chronic substance abuse. These 2 manifestations that are not mutually exclusive, often co-occurring in female substance abusers, have important treatment implications. Research on treatment response for the above clinical presentations is discussed followed by a summary of the factors that may influence sex differences in the association between depression and substance abuse.

Conclusion: Recommendations for future research examining sex differences in animal models of depression, substance abuse, and therapeutic response to medications were made. The need for gender-specific clinical research on the association between depression, stress, and substance abuse is also highlighted.

(J Clin Psychiatry 2002;63:616–627)

Received Aug. 7, 2001; accepted Mar. 13, 2002. From Yale University School of Medicine, New Haven, Conn.

Preparation of this article was supported by grants P50-DA-09241 (Dr. Rounsaville), R01-DA-11077 (Dr. Sinha), and K12-DA14038 (Dr. Sinha) from the National Institute of Drug Abuse, Rockville, Md.

Presented at the Summit on Women and Depression, October 5–7, 2000, Queenstown, Md.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Sinha and Rounsaville have no significant commercial relationships to disclose relative to the presentation.

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Depression is the most common psychiatric diagnosis among substance abusers, and substance abuse is highly comorbid among depressed individuals, second only to anxiety disorders. Sex differences play an important role in the development of depression, and gender differences are found in rates of depression among substance abusers as well. Despite the high co-occurrence of these 2 disorders, the underlying etiology that may link these 2 psychiatric illnesses, particularly in women, remains poorly understood. This article examines the current research on stress and depression and on stress and substance abuse and explores the role that stress may play in linking these 2 illnesses. A literature review was conducted using the keywords *sex*, *gender*, *depression*, and *substance use disorders* for the time period 1980 to the present. Factors that may explain the gender differences in depressed substance abusers are discussed, and treatment options for depressed substance abusers are also presented. Finally, we outline specific gaps in our understanding of the comorbidity of substance abuse and depression in women and provide recommendations for future research.

GENDER DIFFERENCES IN THE EPIDEMIOLOGY, CLINICAL SIGNIFICANCE, AND TREATMENT RESPONSE OF DEPRESSION IN SUBSTANCE ABUSERS

Epidemiology

The trends for sex differences in comorbid mental disorders in substance abusers mirror those for non–drug abusers. To begin with, the majority of individuals with substance use disorders are male,[1,2] with a male:female ratio comparable to that in the opposite direction seen for depression and anxiety disorders.[3] Notable exceptions are nicotine dependence, for which percentages of male and female cigarette smokers are approximately equal, and abuse of prescription drugs, in which females predominate.[4] Within the population of substance abusers, sex differences in patterns of comorbid mental disorders follow the same trends seen in non–drug abusing groups: (1) Female substance abusers are more likely to meet criteria for depression and anxiety disorders.[5–10] They are also more likely to meet criteria for borderline personality disorder.[11–13] (2) Male drug abusers are more likely to meet

criteria for antisocial personality disorder, to use "harder" drugs such as heroin and cocaine, and to be involved with legal problems in association with drug abuse.[6,14] It is noteworthy that antisocial personality does not preclude or prevent depression in drug abusers, and it is strongly associated with depression in this population.[15] Thus, a simple dichotomy of female depressed substance abusers versus male antisocial drug abusers does not cover the complexities of the case.

Other sex difference trends for male/female substance abusers include a later age at first substance use and first substance use disorders for females.[16] However, numerous studies have documented a "telescoping" phenomenon in which female substance abusers experience a rapid progression of illness and a more rapid onset of substance-related physical and social consequences than their male counterparts.[17,18] Within the population of depressed substance abusers, females are more likely to report depression antedating the onset of substance use disorders while depressed males report the onset of depression after onset of substance abuse.[5–7,19] A recently described multivariate typology has led to a distinction among 2 types of substance abusers: (1) a predominantly male type A with an early age at onset, rapid progression of symptoms, high level of dependence, a strongly positive family history of substance use disorders, and sociopathic tendencies; and (2) a type B with an equal distribution in males and females with a later age at onset, slower progression of illness, weaker family history of substance use disorders, and lower sociopathy.[20–22]

Clinical Significance of Substance Abuse in Depression

Depression and vulnerability to substance abuse. The clear gender differences in the manifestation of depression in substance abuse raise important questions regarding the etiology underlying these 2 illnesses in women. Clinical observations have shown that substance abusers, especially women, report depressive symptoms and emotional distress as a common reason for substance use.[23] As depression often antedates the onset of substance abuse in women, it is important to explore this association early in development. Recent evidence indicates that gender differences in lifetime rates of major depression emerge during adolescence.[24] Social factors and hormonal changes during puberty are associated with this sex difference. Adolescent girls show significantly higher rates of depression than boys, and increases in negative affect in adolescent girls are accounted for by an interaction of hormonal changes and stressful life events.[25] Furthermore, in contrast to the epidemiology of substance abuse in adulthood, intriguing gender differences in adolescent substance use have been reported. Unlike in adults, female and male adolescents are equivalent in regular use of substances such as alcohol, nicotine, marijuana, and cocaine in the past year, but females show a greater risk of dependence in adolescence as compared with males, more so than any other age group of women.[26] Whether increased rates of depression are associated with an increased risk of substance dependence in adolescent girls needs future attention in research.

Converging lines of evidence suggest associations between depression, early trauma, posttraumatic stress disorder (PTSD), and increased risk of substance use in adolescent girls and depressed women. First, the rates of comorbidity between depression and substance use disorders (SUD) range from 30% to 50% in adults but appear to be even higher in adolescents.[3,27] Some evidence from a longitudinal study suggests that young adult women with major depressive disorder (MDD) are more likely to have SUD than those without MDD.[28] Progression from initiation of substance use to development of SUD occurs more rapidly in depressed individuals.[29] Furthermore, adolescent substance use is known to escalate in the context of stressful life events, low family support, and peer and parental substance use.[30–33] To the extent the stressful life events are risk factors for both depression and substance abuse in adolescent girls, these data suggest that increased substance use may be associated with a need to regulate affect in adolescent girls.

Second, early life stress, especially sexual abuse, is more common in girls than boys and is significantly associated with risk of developing psychiatric illness and substance abuse, particularly in women.[34–36] Furthermore, adverse life events in adults are clear predictors of psychiatric illness and drug abuse and are more likely to affect women.[37] Animal studies have shown that early life stress increases the sensitivity of laboratory animals to stress, with persistent changes in corticotropin-releasing factor–hypothalamic-pituitary-adrenal (CRF-HPA) responses lasting through adulthood.[38,39] More recent evidence also indicates that such increased responsivity to stress as a result of early life stress is associated with an increased propensity to self-administer abusive drugs such as cocaine in laboratory animals.[40] To the extent that early life stress occurs more frequently in women, it may be one of the possible factors underlying the association between depression and drug abuse in women as compared with men.

Third, although war-related PTSD is a predominantly male disorder, recent surveys have documented that civilian exposure to violence and sexual abuse is much more likely to be reported by women, who are consequently more likely to meet criteria for PTSD.[41–43] Women subjected to violence have been shown to have a higher risk of alcohol and drug dependence.[44] Rates of PTSD and exposure to violence are particularly high in heroin- and cocaine-dependent women seeking treatment.[45] Moreover, alcohol and drug problems place women at risk for repeated assaults.[46] The victimization of substance-abusing

women is likely to be a major contributor to the onset of depression and the perpetuation of substance abuse.

Substantial evidence from preclinical research indicates that uncontrollable stress increases drug self-administration[47–52] and that neurobiological correlates of stress mediate stress-induced increases in drug self-administration.[53,54] Some evidence also suggests that drug self-administration increases significantly in female rats during the estrus phase of the estrous cycle.[55] It is well known that exposure to uncontrollable stress results in behavioral and neurobiological effects consistent with depressive states in animal studies.[56–58] Human laboratory studies have shown that stressful situations in contrast to nonstressful situations lead to increases in smoking and drinking in smokers and social drinkers.[59,60] To the extent that depressive states are more common in women than in men, the above findings suggest that stress and negative affect may increase substance use, possibly more so in women than in men, and at specific points in the menstrual cycle. A controlled examination of this hypothesis has yet to be conducted.

The hypothesis that stress and negative affect increase addictive behaviors is not new. Early theoretical models of addiction have emphasized a key role of stress in increasing drug use.[61–64] For example, the stress-coping model of addiction proposes that use of addictive substances serves to both reduce negative affect and increase positive affect, thereby reinforcing drug taking as an effective, albeit maladaptive, coping strategy.[63] Indeed, the use of substances to self-medicate emotional distress and enhance mood has been a commonly cited reason for drug use.[65–67] More recently, Koob and Le Moal[68] proposed that increasing distress escalates substance use to problematic levels in vulnerable individuals. Animal studies have shown that alterations in the response of brain stress systems can alter the reinforcing efficacy of addictive substances.[69–71] These data are provocative because they suggest that increasing distress may have motivating properties in maintaining drug-seeking behavior not only due to negative reinforcement (relief from negative affect) but also by increasing the effectiveness of the positive drug effects or positive reinforcement. They also provide a possible explanation for findings in the human literature that progression to SUD from initial substance use can occur more rapidly in the context of stress, increasing distress, and depressive states.[29,33,66]

Depression as a consequence of substance abuse. A substantial body of literature indicates that a significant proportion of substance abusers entering treatment report increased levels of anxiety, depression, inability to concentrate, irritability, and impulsivity.[9,72–74] Indeed, substance-induced mood disorders are among the most common comorbid psychiatric diagnoses noted in substance abusers seeking treatment.[9,73] Increased abstinence symptoms, including dysphoria, are associated with treatment attrition and continued drug use in cocaine- and nicotine-dependent individuals.[75–77] Furthermore, gender differences in withdrawal severity have been noted.[23,78]

While substance-induced or "secondary" depression improves with increasing lengths of abstinence,[79,80] studies on the effects of depressive symptoms on treatment retention, treatment success, and relapse to drug use are sparse and somewhat varied by the drug of abuse. For example, several studies have reported better drinking outcomes for women with depression[81–83] and worse drinking outcomes for depressed men.[81] Depression has been shown to be a factor that differentiates opioid and cocaine abusers who seek treatment from those in the community who continue use without seeking treatment.[84,85] These findings have been interpreted as suggesting that painful depression symptoms may help motivate some substance-abusing patients to seek and to become productively engaged in treatment.

In contrast, there is also evidence showing that remission of major depression predicts remission of alcohol dependence, and presence of current major depression is associated with shorter times to first drink and relapse after alcohol treatment.[86,87] Higher levels of depressive symptoms and negative affect are associated with greater urges to use substances in high-risk situations and with time to relapse after inpatient treatment.[88,89] In nicotine dependence, depression has been shown to be a major risk factor for treatment failure. Furthermore, women are more likely to present with comorbid depression and to fail in treatment regardless of depression status.[90,91]

Suicide constitutes an important potential consequence of depression in substance-abusing women. There has been greater recent appreciation of the chronic, relapsing nature of depression and the high rate of eventual suicide in those with major depression.[92] In addition, alcohol and drug abuse are often-replicated risk factors for attempted and completed suicides.[93] Thus, depressed female substance abusers constitute a particularly high-risk, high-prevalence group. Our work suggests that what are described as "accidental" overdoses in drug abusers may represent suicide attempts and may be a marker for depression and other suicidal behaviors.[94]

Treatment of Depression in Substance Abusers

There are no published studies reporting sex differences in depressive symptom response to treatment in substance abusers. However, substance-abusing women are less likely than men to seek treatment in specialized substance abuse treatment facilities.[95,96] Only 1 patient in 4 at substance abuse treatment centers is female. Substance abuse treatment outcome studies also suffer from low representation of women,[97–99] thus hampering examination of sex differences in depressive symptom response. With new evidence showing gender differences in pharmacologic treatment response for chronic major depression,[100]

Table 1. Factors Underlying Sex Differences in Depressed Substance Abusers

A. Differences in personality/psychopathology
   1. Men have higher rates of externalizing disorders characterized by impulsive, dyscontrolled behaviors such as substance abuse and antisocial personality.
   2. Women have higher rates of internalizing disorders characterized by anxiety and depression.

B. Differences in coping responses to stress
   1. Men are more likely to respond with instrumental or activity-oriented coping.
   2. Women are more likely to respond using passive, self-directed strategies for coping.

C. Differences in trauma exposure
   1. Early life stress, particularly childhood sexual abuse, is more common in women than men.
   2. Childhood abuse increases risk of psychiatric illness in women, more so than in men.
   3. Men have higher rates of war-related trauma.
   4. Women have higher rates of civilian violence and sexual abuse. Rates of violent victimization and posttraumatic stress disorder are particularly high in substance-abusing women.

D. Differences in social burdens/social supports of substance abusers
   Substance-abusing women as compared with substance-abusing men are more likely to do the following:
   1. Live with a drug-abusing conjugal partner
   2. Be introduced to drugs by a male partner
   3. Have the sole responsibility of children/minors
   4. Face the negative effects of the social stigma attached to substance abuse

E. Differences in physiologic effects of abusive drugs
   Alcohol:
   1. For the same amount of alcohol consumed, women report high levels of intoxication and reach those levels more quickly.
   2. Women face greater physiologic impairment from alcohol use earlier in their drinking history and despite consuming less alcohol than men.

   Cocaine:
   1. Women consume similar quantities of cocaine but experience more rapid progression to dependence than men.
   2. Smoked cocaine produces similar subjective effects in women but prolonged cardiovascular effects and higher cocaine plasma concentrations as compared with men.

   Nicotine:
   1. Women smoke fewer cigarettes and inhale less intensely than men.
   2. Women metabolize nicotine more slowly than men, resulting in greater total exposure.
   3. Women experience greater/sustained nicotine withdrawal symptoms compared with men.

F. Differences in psychobiology of stress and depression
   1. Women report higher levels of subjective anxiety but lower hypothalamic-pituitary-adrenal (HPA) response to stress than men. The HPA responses vary as a function of the phase of the menstrual cycle.
   2. Depressed women show greater HPA axis dysregulation as compared with depressed men and healthy controls.

gender influences in depression symptom reduction in substance abuse needs further exploration. Nonetheless, there is some evidence that treatment of depression with antidepressants in substance abuse facilities appears to confer some benefit in outcomes.

Controlled pharmacologic trials of treatments for depressed substance abusers support the efficacy of antidepressant medications in reduction of depressive symptoms,[101] particularly when treating patients with primary depression.[102,103] In addition, improved substance use outcomes in response to antidepressant treatments have been less frequently demonstrated.[101] However, the evidence for efficacy of antidepressant medications in substance abusers is less robust than that derived from depressed individuals without substance abuse comorbidity. One likely cause for this trend pertains to challenges in diagnosing current major depression in drug abusers, particularly in distinguishing between depression that is substance induced and that which is independent of substance effects. Individuals whose depression is substance induced are likely to recover when substance abuse discontinues and without antidepressant pharmacotherapy. Inclusion of substantial numbers of patients with substance-induced depression in antidepressant trials may undermine the detection of true treatment effects.[104,105] To deal with this issue, structured diagnostic interviews including the Psychiatric Research Interview of Substance and Mental Disorders[106] and a modification of the Structured Clinical Interview for DSM-IV Disorders[107] have been developed to document the relationship between depression and substance use patterns, but these have seldom been employed in clinical trials.

In contrast to recent findings of gender differences in response to pharmacologic treatment of depression,[100] very few sex differences in response to nonpharmacologic, psychosocial treatment of depression have been observed. Some studies have examined the benefit of conducting cognitive-behavioral therapy with mood management for groups of depressed smokers and depressed alcoholics.[88,108] While these studies report improvements in nicotine and alcohol abstinence rates with cognitive-behavioral mood management, there has been little examination of sex differences in the effects of cognitive-behavioral mood management on abstinence rates. An exception is a study by Hall and colleagues[109] which found that while smokers with a history of depression were more likely to benefit from cognitive-behavioral mood management therapy, this was not true for women with depressive histories. Clearly, there is a need to examine sex differences more carefully in treatment studies of patients with comorbid depression and substance abuse.

FACTORS POTENTIALLY UNDERLYING SEX DIFFERENCES IN DEPRESSED SUBSTANCE ABUSERS

Several factors are associated with sex differences in depressed substance abusers. These are described below and summarized in Table 1.

Personality, Psychopathology, and Coping Strategies

Sex differences in depressed substance abusers represent a special case of general trends for sex differences in studies of psychopathology, personality characteristics,

and coping strategies. To sum up the sex difference trends in the epidemiology of mental disorders, men have a preponderance of "externalizing" disorders characterized by impulsive, dyscontrolled behaviors such as substance use disorders and antisocial personality disorder.[110,111] In contrast, women have higher rates of "internalizing" disorders characterized by painful symptoms that have been analogized to "defensive" behaviors in female rodents,[112,113] including anxiety disorders and depression. These mental disorder trends are parallel to differences in norms for widely validated personality dimensions such as neuroticism, for which women tend to score more highly, and extraversion and sensation seeking, for which the male norms are higher. Sex differences in the literature on coping strategies provide further confirmation of the "externalizing" and "internalizing" trends, as men tend to respond to stress with instrumental or activity-oriented coping strategies while women report using more passive, self-directed strategies.[114] These general trends can be understood in women as related to increased risk factors for depression and protective factors for substance abuse and antisocial personality. The factors underlying these larger trends are likely to include cultural as well as biological determinants. For example, higher rates among females of disapproval for driving while intoxicated (DWI) have been noted as a contributor to the predominance of males in rates of DWI arrests.[115]

Women substance abusers embody exceptions to these trends because they meet criteria for both a male-predominant "externalizing" disorder (i.e., substance abuse) and a female-predominant "internalizing" disorder (i.e., depression). Given the comparative protection of women from becoming substance abusers, the threshold for women to develop drug abuse is assumed to be higher than that for men. According to the reasoning behind this "threshold effect," it is assumed that women would need to accumulate more risk factors in order to cross the barriers otherwise protecting them from substance abuse. These factors can include exposure to drugs, genetically transmitted vulnerability, stress, lack of social supports, and comorbid psychopathology. For depressed female drug abusers, the high rate of primary depression suggests that a prior mood disorder pushed them over the threshold into drug abuse.

Social Burdens and Social Supports of Substance Abusers

In comparison with male drug abusers, female drug abusers are more likely, at the time they seek treatment, to be living with a drug-abusing conjugal partner, a major risk factor for treatment failure.[6,116] In the natural history of substance use disorders, women are more likely than men to be introduced to drugs by a drug-abusing sexual partner while men are more likely to be initiated by other male peers.[117] In addition, treatment-seeking female drug abusers are more likely to be responsible for the care of minor children.[118,119] Such responsibilities can be a protective factor, providing motivation to seek treatment and become drug free, but it can also place heavy burdens on drug-abusing women related to logistics of coming to treatment or demands that prevent vocational and educational rehabilitation.

Stigma is a factor likely to reduce treatment seeking, exacerbate depression, and impede recovery of depressed female substance abusers. As being a drug-abusing woman is less common and is often considered more socially deviant, female drug abusers are prone to attracting greater attention from their own and other social groups and to be even more stigmatized than men with the same disorder.

Substance Abuse, Sex Hormones, and the Reproductive Cycle

Notably, drugs and alcohol have different physiologic effects on women and men. For example, after consuming the same amount of alcohol, women become more intoxicated and intoxicated more quickly.[120] They go on to experience greater physiologic impairment earlier in their drinking history, despite having consumed less alcohol than men.[96,121] A number of studies have also begun to show variations in drug effects across the menstrual cycle. For example, response to intranasal cocaine administration in women has been found to result in higher mean plasma cocaine levels during the follicular than the luteal phase.[122] With regard to stimulants, including cocaine, female rodents exhibit greater stimulant-induced activity, which also varies with the estrous cycle.[123] Moreover, female animals have been shown to self-administer cocaine at a higher rate than males, and rates of self-administration vary with the estrous cycle, with higher rates in the follicular than the luteal phase.[123]

In humans, a number of key findings suggest an impact of cocaine and opioids on female sex hormones and on the reproductive cycle that can be highly disruptive and hazardous to health.[124] A particularly disturbing observation is the high rate of relapse to smoking and other substance use disorders among women who refrain from substance use during pregnancy.[125] The potential impact of postpartum mood changes on this substance abuse relapse has been little examined. Furthermore, there is some evidence to suggest that women smokers who enter treatment in the premenstrual phase of their cycle may be more likely to drop out of treatment and unable to achieve abstinence from nicotine.[126] We have recently found the same to be true for opiate-addicted women entering naltrexone treatment for opiate addiction (R.S.; M. Hayes, B.A.; I. Hogan R.N.; manuscript in preparation). Whether such differences in drug-seeking behavior and treatment response are associated with varying levels of steroid hormones or alterations in mood or both in drug-addicted women needs further systematic study.

Psychobiology of Stress, Depression, and Drug Use

The psychobiology of stress. Sexual dimorphism in the psychobiology of stress has been frequently reported. While in rodents HPA response as measured by adrenocorticotropic hormone (ACTH) and cortisol levels is greater in females than males,[127,128] the picture is more complex in humans. In general, women report higher levels of subjective anxiety in stressful situations but show a lower HPA response as measured by ACTH and cortisol to biological and psychological stress as compared with men.[129] However, these differences vary by phase of the menstrual cycle, with the variations presumably associated with changing levels of steroid hormones. For example, lower HPA and adrenergic response to psychological stress has been reported during the follicular phase, while the psychoendocrine stress response is higher in the luteal phase.[130] Furthermore, administration of estrogen in men increases their stress-induced cortisol response.[131] Using pharmacologic challenges to probe HPA axis regulation, Young[132] found a 40% greater cortisol response to corticotropin-releasing hormone (CRH) administration in women as compared with men. Thus, estrogen and possibly progesterone appear to modulate the HPA axis response to stress in humans.

Sex differences in HPA axis regulation and depression. Abnormalities of the HPA axis as manifested by hypercortisolemia and disruption of the circadian rhythm of cortisol secretion are well-established phenomena in depression.[133,134] Depressed patients are also less likely than control subjects to suppress ACTH and cortisol secretion after receiving dexamethasone, a synthetic analogue of cortisol.[135] However, depressed women are more likely than men to exhibit these HPA axis regulation abnormalities.[134] Depressed women show increased cortisol secretion as compared with female controls and depressed men, with increased central HPA drive in the evening.[128] While these data suggest greater HPA axis dysregulation in depressed women, and previously cited evidence suggests that stressful life events in vulnerable women increase the likelihood of onset of a depressive episode, the mechanism by which coping with stressful life events interacts with HPA axis regulation and hormonal levels is not well understood. Future studies that examine ways in which acute and chronic distress interacts with HPA axis regulation in women to produce depressive states are needed to fully understand the association between the psychobiology of stress and that of depression.

Stress, drug self-administration, and drug relapse. A growing body of preclinical evidence has begun to elucidate the mechanisms underlying the association between stress and drug self-administration. As cited earlier, several animal studies have shown that exposure to acute stress increases drug self-administration.[47–54] In addition, exposure to uncontrollable stress also reinstates drug-seeking behavior in drug-addicted animals who were drug free for over 6 weeks.[136–138] This stress-reinstatement paradigm has provided a novel animal model of drug relapse. These studies have demonstrated that acute behavioral stress is equivalent to the drug itself in its potency to reinstate drug-seeking behaviors.[54] We have recently shown that laboratory induction of stress via imagery of personal stressful events significantly increases drug craving in cocaine- and alcohol-dependent individuals.[139,140] Based on previous evidence linking stress and depression and also depression and drug use in women, there is good reason to postulate that stress-induced increases in drug craving and their neurobiological correlates vary as a function of gender and depression.

The role of the stress hormone CRH and its stimulation of the HPA axis during stress and drug-seeking behavior have also been studied. Some evidence suggests that increased levels of circulating glucocorticoids (cortisol), a common response to uncontrollable stress and depressive states, is a key mediator of stress-induced drug-seeking behavior.[48,53] However, others have shown that stress-induced relapse is not associated with increased levels of glucocorticoids, but rather involves the actions of brain CRF and noradrenergic systems.[54,141,142] Whether it is circulating glucocorticoid levels or brain CRF and noradrengeric systems or both that mediate drug-seeking behavior and relapse in humans is yet to be determined. Furthermore, as sexual dimorphism in HPA axis regulation and stress reactivity, especially as it pertains to manifestation of depression in women, has been documented, the question of whether such gender differences may significantly impact stress-induced drug-seeking behavior in humans appears worth pursuing in future research.

Table 2. Recommendations for Research in Women With Comorbid Depression and Substance Abuse

A.	Increase attention to sex differences in animal research by requiring female representation in National Institutes of Health proposals, particularly in substance abuse, depression models, and response to therapeutic agents.
B.	Heighten attention to sex differences in clinical research, including development of efficient methods for monitoring female subjects with regard to menstrual cycle status in clinical trials.
C.	Evaluate strategies to improve treatment access in substance-abusing women.
D.	Promote research on sex differences in the association between acute and chronic stress, depression, and substance abuse.
E.	Develop specific behavioral and pharmacologic interventions that target depression and substance abuse in women, with particular focus on stress regulation.

RECOMMENDATIONS FOR PROMISING RESEARCH DIRECTIONS

Recommendations for research in women with comorbid depression and substance abuse are summarized in Table 2 and described in detail below.

Make Sex Differences a Focus of Basic/Animal Studies of Drugs, Depression, and Response to Therapeutic Agents

Female animals have been excluded from much of the basic work pertaining to depression and substance abuse. This exclusion is likely related to difficulties in controlling the effects of the estrous cycle and fluctuating levels of female sex hormones. However, these "complications" may provide a fruitful avenue into unexpected findings pertaining to the importance of sex differences and sex hormones for depression, response to abused substances, and response to therapeutic agents. The work by Roberts and colleagues[123] demonstrating sex differences in rats' cocaine self-administration is particularly illustrative of the potential for such an approach. There is now growing animal research documenting sex differences in a number of pertinent pairs of variables including sex differences in stress response, sex differences in anxious and depressive behaviors, and sex differences in response to abused substances.[143] However, little research has examined 3- and 4-way interactions, such as the relationship between sex differences, stress response, depression, and substance use. We recomend the following:

- Attention to sex differences in animal research should be heightened by requiring female representation in basic National Institutes of Health research proposals or a justification for the exclusion of female animals.
- Greater attention should be focused on developing methodologies for research on complex interactions among factors related to the sex differences, substance abuse, and depression.

Heighten Attention to Sex Differences in Clinical Research

Requiring representation of women and minorities in clinical research on substance abuse and other mental disorders has been an important step in facilitating the discovery of sex differences in treatment response and drug effects. A major problem in the drug abuse treatment field is that, except in large, phase 3 trials, the number of female subjects in clinical studies still tends to be small, such that separate, sex-related analyses are undermined by lack of adequate statistical power.

The findings of Roberts and colleagues[123] regarding variability in cocaine effects and rates of self-administration across the rodent estrous cycle are particularly provocative because they highlight a potentially important and largely unstudied source of variability. Such variability could have a major impact in research on the effects of therapeutic medications for depression and substance abuse and on treatment strategies for female drug abusers. To date, almost no studies of pharmacotherapies for depression in substance abusers have addressed sex differences, let alone differences in women's response to treatment in relation to their phase in the menstrual cycle. If these findings generalize to humans, they suggest that efficacy of pharmacotherapies may be optimized by coordinating their initiation and dosage with the most conducive time in the menstrual cycle. If craving is highest during the premenstrual period, timing of "quit dates" for cigarettes or other psychoactive substances might be pinpointed to the follicular or early luteal phase instead. While these possibilities are intriguing, they remain speculative in large part due to the lack of attention to menstrual cycle phase in female substance abusers participating in treatment and clinical laboratory studies of effects of abused or therapeutic drugs. We recommend the following:

- Research on the relationship of the menstrual cycle to drug effects and treatment response should be expanded. To that end, efficient, accurate methods should be made available to monitor female subjects' phase in the menstrual cycle and routinely utilized in clinical trials and other clinical studies of substance abusers.

Evaluate Strategies to Improve Treatment Access/Efficacy in Women

Substance-abusing women who do seek treatment are more likely to complete it and may experience more benefit as compared with men.[144–146] However, the general population of substance-abusing women may be underserved because they are less likely than men to enter traditional substance abuse programs. Hence, research on improving treatment of substance-abusing women may most profitably focus on strategies that target those not in treatment. We recommend several lines of research designed to enhance the efficacy of substance abuse treatment for depressed women:

- Improved methods for detecting and diagnosing substance abuse should be evaluated in agencies where women are likely to be seen, such as primary care medical clinics, mental health centers, obstetrical clinics, welfare agencies, and legal settings.
- Strategies for providing substance abuse treatment integrated with other services, such as primary medical care and mental health services, may be particularly effective for substance-abusing women who are reluctant to enter male-oriented specialty programs.
- Surveys on attitudes toward quitting substance use and entering treatment conducted with untreated samples of women could point to ways to motivate them to seek care.
- In traditional specialty treatment programs, treatment for women could be improved by sex-

specific revisions in format (e.g., all-women's groups), content (e.g., attention to parenting issues[147]), and strategies (e.g., insight-oriented vs. cognitive-behavioral[148–150]).

Promote Research on Sex Differences in Psychobiology of Stress in Depression and Substance Abuse

We have outlined in this article previous research that shows an association between neurobiological stress systems such as the CRF-HPA axis and the noradrenergic systems and depression, as well as drug-seeking behavior. Furthermore, evidence suggesting that the reproductive hormones modulate the stress response and HPA axis regulation is cited. However, research on the ways in which sex differences in stressful life events and stress reactivity interact with depressed affect and drug-seeking behavior is lacking. Given the renewed importance of the role of stress in escalating drug use and drug-seeking behavior/relapse in addicts, we recommend several promising research directions in this area:

- Sex differences in history of early trauma, adverse life events and their impact on depression, and drug use in both addicted populations and vulnerable "at-risk" populations need further study.
- Psychobiological studies on how stress increases depressed affect and/or drug-seeking behavior in "at-risk" and addicted individuals would be useful in understanding the mechanisms underlying the association between stress, depression, and substance use.
- Whether changes in reproductive hormone levels alter drug-seeking behavior and relapse patterns in substance-abusing women needs future examination as well. Such information can be of significance in developing women-specific substance abuse treatments.
- While sex differences in HPA axis regulation have been studied in depression, ways in which acute and chronic psychosocial stress alter brain stress systems need clarification in future studies. Such research can be useful in identifying specific stress-related vulnerabilities in women at risk for recurrent episodes of depression.

Address Both Depression and Substance Abuse in Women, With Treatments Aimed at Stress Reduction and Improved Coping

On the basis of evidence cited in this article on the clinical significance of depressed affect in substance abuse, there appears to be a good rationale for addressing negative affect in substance abuse treatment. However, standard substance abuse treatments primarily focus on avoidance of drug use and coping with high-risk situations, with only secondary emphasis on stress management and negative affect reduction.[149,150] This may be the reason that state-of-the-art psychosocial treatments for substance abuse do not show specific efficacy for substance abusers with moderate-to-high psychiatric severity.[99,148]

Although Hall and colleagues[151] have shown that cognitive-behavioral mood management intervention increases nicotine abstinence in nicotine-dependent smokers with depressive histories, women with depressive histories were less likely to be abstinent from nicotine with either pharmacologic or psychosocial treatment.[109] While this line of research has begun to target depression in nicotine dependence, behavioral interventions that target depression and negative affect in other types of drug abuse, especially in substance-abusing women, are lacking. We recommend the following line of research to address this gap:

- There is a need to translate research from basic human studies of stress and coping to the development of clinical interventions that target stress regulation and improved coping with distress. As stress and coping resources play a key role in drug-seeking behavior, we suggest that new interventions that target stress regulation need to be explored. Development of such treatments could be of specific benefit to substance-abusing women.

CONCLUSION: WHAT DOES A DRUG ABUSE PERSPECTIVE BRING TO THE STUDY OF WOMEN AND DEPRESSION?

Drug (particularly nicotine) and alcohol abuse and dependence are associated with depression in women. Generally, investigators primarily interested in depression have considered the role of substance abuse in depression as a nuisance factor that is handled by excluding subjects with current substance use disorders from studies of pharmacotherapy and neurobiology of depression. However, in this article we have outlined previous evidence to suggest that specific research on the association between the 2 disorders may tell us unexpected things about either or both of these disorders. When the 2 disorders are associated, there are 3 general (nonexclusive) models explaining the association: (1) depression may cause substance abuse, (2) substance abuse may cause depression, or (3) both may be related to a third factor.

For women more than for men, there is evidence for the first model, as depression in female drug abusers is more likely to be primary and longitudinal studies show increased risk of drug use and misuse in females who initially report dysphoric mood but no prior drug use. Animal studies of drug self-administration show greater stress-induced opiate use in females than males. Depressed

female cigarette smokers have an especially poor prognosis for smoking cessation. In contrast, the preponderance of secondary depression in males supports the second model and suggests that depression may arise more from pharmacologic effects or psychosocial consequences of drug dependence. Regarding the third model, the preponderance of evidence from family and genetic studies suggests independence in transmission of vulnerability to substance abuse and depression.[152] These findings fail to support the possibility that a shared third genetic or familial factor underlies both disorders, further underscoring the need to explore environmental factors such as stressful life events, coping abilities, and hormonal influences that may operate to link depression and substance abuse in women.

The evidence that depression is more likely to lead to substance abuse in women points to an intriguing set of questions. What is it about the nature of depression or stress response in females that makes "self-treatment" with drugs more likely? Are there hormone-related sex differences in the neurobiology of depression in women that sensitizes them to effects of nicotine or opiates? Are there beneficial effects of abused substances, such as nicotine, that could be targeted in new medications that have fewer addictive properties? Do women need antidepressant medications that are different from those effective for men, and should these medications share more properties with addictive substances? Clearly, future research to answer these key questions is critical, both to increase our understanding of these disorders and to improve treatments for depression and substance abuse in women.

Drug names: dexamethasone (Decadron and others), naltrexone (ReVia).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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