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Dual Depression: A Sex Perspective

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Abstract

Mood and substance use disorders (SUDs) are mental conditions that are highly prevalent in the general population. Cooccurrence of major depression and SUD, also known as dual depression, is very common in the field of substance addiction. Sex differences are found in both major depression and SUD. This review, after presenting the state of the art of dual depression as regards prevalence, ethiopathologic mechanisms, and clinical aspects, is focused on dual depression in women. An overview of some potential factors associated with the sex gap in dual depression such as injecting, sexual risk behavior, intimate partner violence, and the reproductive cycle is presented.

Key Words: depression, dual pathology, comorbidity, women, recommendations, substance use disorder, dual depression

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Mood and substance use disorders (SUDs) are mental illnesses that are highly prevalent in the general population and are known to be among the leading causes of the global disease burden.[1] Sex differences are found in both major depression (MD) and SUD: a higher incidence of depressive disorders has been reported for women,[2] whereas SUD are more prevalent in men.[3] The cooccurrence of MD and SUD, also denominated dual depression, is very common[4] and worsens the prognosis of patients with a poor response to the treatment of both disorders.[5,6] To date, there has been limited evidence concerning dual depression among women. In this review, after presenting the state of the art of dual depression with respect to prevalence, ethiopathologic mechanisms, and clinical aspects, we will focus on this condition in female individuals and some potential factors involved in the sex gap observed.

DUAL DEPRESSION: AN OVERVIEW

Epidemiological Data

The prevalence of dual depression varies from 12% to 80%.[7–9] Such a wide range can be explained by a number of factors, the most relevant being the characteristics of the sample studied (general population, patients seeking treatment in addiction/mental health facilities or elsewhere such as prisons, homeless individuals); the main substance of use (alcohol, tobacco, cocaine, opiates, sedatives, cannabis); the diagnostic criteria employed (Diagnostic and Statistical Manual of Mental Disorders-DSM or International Classification of Diseases-ICD in its different versions); and the diagnostic tools used (such as the Psychiatric Research Interview for Substance and Mental Disorders(PRISM), the Structured Clinical Interview for DSM-SCID, Schedules for Clinical Assessment in Neuropsychiatry-SCAN, and screening interviews such as the Dual Diagnosis Screening Instrument-DDSI). In a systematic review and meta-analysis of epidemiological studies in the general population between 1990 and 2014, the strong association between depression and SUD was confirmed.[10] This association was greater for illicit drugs [odds ratio, 3.80; 95% confidence interval (CI), 3.02-4.78] than for alcohol (odds ratio, 2.42; 95% CI, 2.22-2.64) and was stronger for disorders with dependence disorder criteria than for abuse, irrespective of whether it was based on lifetime prevalence or during the previous 12 months. As expected, in nonsubstance users (wherein MD is more frequent in female individuals)[11] and in SUD subjects, comorbid MD is twice as common in women as in men. Interestingly, in women diagnosed with SUD, cooccurrent MD is more frequent than in those without SUD; therefore, female individuals with SUD are a particularly vulnerable group for MD.[12,13] Furthermore, in female illicit drug users, primary MD was more common (17%) than substance-induced depression (10%). Being a female individual and

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having a lifetime borderline personality disorder doubles the risk of presenting independent disorders.[13]

In a study of 162 patients with alcohol addiction, the prevalence of comorbid psychiatric disorders was higher in women (82.5%) than in men (63.9%), with comorbid MD being significantly elevated among the former (67.5% vs. 38.5%).[14] In addition, it was observed that although women start drinking later than men, they take less time to develop dependence symptoms and meet fewer severity criteria than men. In a sample of 55 abstinent cocaine-addicted participants with lifetime cocaine use disorders (15 women and 40 men), women had an increased prevalence of comorbid psychiatric disorders, with 53.3% of them reporting mood disorders in comparison with 32.5% in men.[15]

More specifically, women who inject drugs (WWID) constitute a particularly vulnerable group. Injecting, sexual risk behavior, prostitution, intimate partner violence (IPV), bloodborne virus infections, and psychiatric disorders are experiences and adverse health outcomes frequently found in this population. A recent study included a total of 226 female individuals who had injected drugs in the past 6 months, recruited in both treatment and harm reduction facilities from 5 European countries. The majority of participants (87%) screened positive for at least 1 lifetime psychiatric disorder. The most common conditions were depression (76%), panic (54%), and posttraumatic stress disorder (PTSD) (52%). WWID and girls who inject drugs, who were recruited from drug treatment facilities were almost 3 times as likely (OR, 2.89; 95% CI, 1.30-6.43; $P = 0.007$) to meet the criteria for a lifetime psychiatric disorder than those recruited from harm reduction ones. The principal differences were found in dysthymia (OR, 5.32; 95% CI, 2.27-12.48; $P = 0.000$) and PTSD (OR, 1.83; 95% CI, 1.02-3.27; $P = 0.040$).[16]

Etiopathologic Mechanisms

The high concurrence of MD and SUD can be explained mainly by 3 nonexcluding hypotheses: (a) SUD and MD share the same common risk factors, such as stressful life events, psychological trauma, genetic vulnerability, and/or neurobiological alterations leading to the appearance of both disorders, without a causal relationship between them; (b) the continued use of certain substances leads to neurobiological changes through neuroadaptative mechanisms that mediate MD; and (c) SUD develops to relieve MD (self-medication hypothesis).

In both disorders (MD and SUD), genetic and environmental factors are essential in facilitating neurobiological mechanisms related to pathogenesis.[17] The main molecular mechanisms involved in the neurobiology of depression include those of the monoaminergic system, the hypothalamic-pituitary-adrenal system, the immunologic system, central nervous system neurotrophic factors, the endocannabinoid system, circadian rhythms, food intake, the metabolism system, and gut microbiota.[18–22] The majority of these also play a role in the development of SUD[17,20,23] and alcohol-induced liver injury.[24] Significantly, the brain reward circuits, which are implicated in the pathogenesis of addiction, are additionally involved in the neurobiology of depressive disorders.[25]

Clinical Aspects

The diagnosis of MD in a current drug-using patient is principally hindered by the acute or chronic effects of substance use (both chronic intoxication and withdrawal), which can mimic depressive symptoms. According to the DSM-5, in an SUD patient, a distinction must be made between (i) a primary MD disorder, (ii) expected effects of drug intoxication/withdrawal, and (iii) an induced MD disorder (Table 1).

It is important to note that, in the case of SUD, because of cocaine, opiate, or polydrugs, an MD episode usually occurs frequently, irrespective of consumption,[13] whereas, in the case of alcohol, a higher prevalence is described in association with induced depression.[26] Both types of depression (primary and induced) can be found in the same patient.[27]

Furthermore, the coexistence of SUD and MD has been associated with

TABLE 1. Primary, Induced, Expected Effects

Diagnoses	Definition
Primary	Mental disorders that are not induced by substances or arising from medical illness,eg, independent disorders
Substance induced	Disorders that seem to be in relation with substance use or withdrawal but can be considered excessive with regard to the expected effects
Expected effects	This refers to symptoms considered specific to intoxication or withdrawal from a given substance, which should therefore not be taken into account as symptoms for diagnosing depression (eg, insomnia during acute stimulant poisoning or during a period of opiate withdrawal)

an unfavorable course of both diseases, with worse response to treatment and poorer prognosis.[4,6] Thus, follow-up studies in user patients have observed that the presence of depressive episodes, both primary and induced, strongly facilitate consumption relapse.[28,29]

Several studies have also observed that SUD and MD comorbidity increases clinical severity and the risk of suicidal behavior.[30,31] In addition, these patients are more likely to develop other medical comorbidities, making treatment even more difficult. As is expected from their marked clinical severity, such individuals also show considerably poorer psychosocial function and make greater use of health resources, including emergency services and psychiatric hospitalizations.[5,29,32,33] Moreover, it has been reported that patients with MD are twice as likely to develop 1 SUD, just as those presenting an SUD have twice the risk of suffering an MD throughout their lives.[34]

DUAL DEPRESSION IN FEMALE INDIVIDUALS

The higher prevalence of depression in female individuals than in male individuals has been well established.[11] A number of potential risk factors that may explain the difference in estimated MD prevalence between both genders in the general population have been recently reviewed by Kuehner. Table 2 summarizes the possible factors at 3 different levels: biological, psychological, and environmental.[35]

Focusing on dual depression in women, the present review has centered mainly on the association of dual depression and injecting, sexual risk behavior, IPV, and the reproductive cycle.

Injecting and Sexual Risk Behavior

In contrast to men, female drug users present greater psychopathology and risk behavior, which increase the probability of human immunodeficiency virus (HIV) and hepatitis C virus infection.[36,37] Sharing needles and injecting paraphernalia, reporting sexual

TABLE 2. Potential Factors Involved in the Sex Gap in Depression Based on Kuehner[35]

Biological Factors	Psychological Factors	Environmental Factors
Genetic risk	Neuroticism and negative affect	Early adversity: childhood sexual abuse
Gene-environment interactions	Absence of positive affect	Interpersonal violence after childhood
Hormones	Interpersonal orientation	Common life events: exposure to stress
Physiological stress response	Rumination and corumination	Common life events: susceptibility to stress
	Body shame and dissatisfaction	Societal structural sex inequities

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risk behavior, exchanging sex for money or drugs, and not using condoms are considered risk behaviors that put women at greater danger of HIV/hepatitis C virus transmission.[38] The literature has reported that depression among WWID is associated with injection risk behavior such as sharing needles.[39] Evidence-based psychosocial interventions have described reductions in injecting/sexual risk behavior and depressive symptoms among female drug injectors[37]

IPV

Young women experience a greater number of interpersonal stressors than men.[40] Histories of psychiatric disorders, IPV, and childhood abuse are common in female substance users under treatment. Research suggests that such backgrounds result in poorer treatment outcomes. The relationship of IPV, childhood abuse, and psychiatric disorders in 118 female drug users under treatment in Barcelona was evaluated.[41] The probability of experiencing IPV was more than 2-fold greater among those with any depressive disorder, and over 3 times greater for those who reported attempting suicide, met criteria for borderline personality disorder, or had been abused in childhood. Experiencing violence is considered one of the most important psychosocial risk factors for psychiatric disorders in women.[42]

Furthermore, IPV victims seeking treatment for SUD are more likely to experience drug-taking risk behavior, which may be explained by the negative influence/control of the perpetrator,[43] thus increasing the danger of HIV/Hepatitis C.

Reproductive Cycle

The reproductive cycle is a crucial phase in which many women may experience MD, including premenstrual dysphoric disorder, partum and postpartum depression, and menopausal depression. Maternal depression is one of the major contributors to pregnancy-related morbidity and mortality. Perinatal depression in low-income and middle-income countries is highly prevalent, affecting about 1 in 4 women antepartum and 1 in 5 postpartum. In a recent review, the pooled prevalence estimate of antepartum depression was 25.3% (95% CI, 21.4-29.6) across 51 studies and that of postpartum depression was 19.0% (95% CI, 15.5-23.0) across 53 studies. Maternal depression (antepartum and postpartum) has been linked to negative health-related behavior and adverse outcomes, including psychological and developmental disturbances in infants, children, and adolescents.[44]

Alcohol and other drug use during pregnancy is a major risk factor for maternal morbidity and neonatal complications. Tobacco consumption is associated with spontaneous miscarriage, fetal growth restriction, and preterm delivery. Heavy caffeine use may be linked with first-trimester loss. The misuse of alcohol has a significantly potential impact on pregnancy with fetal alcohol spectrum disorder being the most severe. Opioids and sedative hypnotics may not be strongly associated with teratogenicity, but fetal sedation and withdrawal at the time of delivery is a consequence of their long-term effects. Methadone, morphine, and buprenorphine maintenance are suggested for opiate-addicted pregnant patients.

Approximately half of the patients suffering from an SUD or alcohol-related disorder also match the criteria for some other psychiatric condition, although little is known about comorbidity among substance-misusing pregnant women. In a sample of 49 pregnant women with SUD in Finland, 57% of the substance-misusing ones had psychiatric illnesses. In the comorbid group, depression (43%) and anxiety disorders (36%) were the most common diagnoses.[45] In a prospective study of a cohort of 4447 substance-using mothers (pregnant or parenting) who were enrolled during 2000 to 2002 in drug-abuse treatment programs, the participants had 8.4 times greater mortality than that observed among women of a similar age who were not substance abusers. Drug overdose (28.8%), cardiovascular disease (10%), and alcohol or drug disorders (8.9%) were the leading causes of death. Greater difficulties with employment, medical issues/health, and psychiatric problems contributed to the elevated mortality. The deceased women were found to have

had a greater number of psychiatric symptoms (eg, depression, anxiety, and hallucinations) and to have received more prior inpatient psychiatric treatment.[46]

In the United States, in a sample of 502 female adolescents and adults with SUD who reported having been pregnant in the previous year, the prevalence of coocurring mental disorders was 91.3%.[47]

Postpartum mood disorders affect ~10% to 20% of women and have adverse consequences for both mother and baby. However, lifetime substance use has received limited attention in relation to this issue. Prevat et al studied the associations of lifetime alcohol and drug use with postpartum mental health problems among 100 women for ~3 months.[48] Their findings suggest that lifetime substance use increased the variability explained in postpartum PTSD ($P = 0.011$) above and beyond sociodemographic characteristics and mental health history. Lifetime drug use was specifically associated with postpartum stress ($P = 0.021$) and anxiety ($P = 0.041$), whereas lifetime alcohol use was not ($Ps \geq 0.128$). The results suggest that lifetime drug use is associated with postpartum mood disorders.[48]

TABLE 3. Clinical and Social Characteristics among Women with Dual Depression

Main Characteristics of Dual Depression in Female Individuals
Comorbid MD in SUD is more prevalent in women than in men
Comorbid MD in women is more frequent in primary than in substance-induced depression
Women with comorbid MD and SUD present greater risk of experiencing intimate partner violence
Comorbid MD in women is associated with higher risk behavior for HIV, HCV infection
Higher prevalence of perinatal depression in female individuals with SUD
Higher prevalence of postpartum mood disorders among pregnant women with SUD

HCV indicates hepatitis C virus; HIV, human immunodeficiency virus; MD, major depression; SUD, substance use disorder.

CONCLUSIONS

Dual depression is more prevalent in women than in men and more frequent than expected in women without any SUD. A number of risk factors may help to explain the sex differences. Women with SUD report a high occurrence of injecting and sexual risk behavior, prostitution, and IPV, which are experiences associated with dual depression.

Because of the dual diagnoses, patients present greater medical severity (higher risk to be HIV and HCV infected), worse social functioning, and poorer response to treatment and prognosis. The treatment of dual depression should take into account the prevalence of these risk factors in female drug users in order to develop the most appropriate approach (Table 3).

Research and practice should consider all these risk factors in order to improve diagnosis and have more effective treatment options for these patients. In addition, biological factors in dual depression should receive greater attention in order to obtain firm conclusions regarding their influence. More longitudinal studies are required to establish the directionality of the factors affecting MD and SUD in women.

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