Substance Use Disorders: Sex Differences and Psychiatric Comorbidities

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Objective: This article reviews sex differences in psychiatric comorbidity among individuals with substance use disorders and, in particular, the clinical significance of these differences for treatment outcome among women.

Method: We undertook a computerized search of major health care databases. To enhance the search, we drew prior relevant articles from the reference list.

Results: Women with alcohol and other drug use disorders present higher rates of psychiatric comorbidity, particularly mood and anxiety disorders, than do men. Moreover, the comorbid diagnosis, particularly of depression, is more often primary in women, while in men the comorbidity is more often secondary to the substance abuse diagnosis. In addition, there is evidence that psychiatric comorbidity is associated with distinct, sex-specific outcomes for substance use treatment.

Conclusions: Sex differences in the clinical presentation of substance-dependent individuals with psychiatric comorbidity present specific treatment challenges and opportunities.

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Clinical Implications

Women with substance use disorders present higher prevalence rates of psychiatric comorbidity than do men with the same diagnosis, making the psychiatric assessment a crucial step in evaluating women seeking treatment for a substance use disorder.

Among women, major depression is more often primary to the substance use disorder (with the opposite occurring in men); it is therefore less likely to improve with abstinence from psychoactive substances alone and often requires specific treatment.

Women with primary depression or anxiety disorders should be followed carefully and taught to recognize early signs of recurrence. Vigorously treating a recurrence of depression can prevent full relapse of the substance use disorder.

Limitations

Although there is some indication that the comorbidity of alcohol use disorders and depression may imply a better treatment outcome for women, but not for men, more studies are needed to confirm this issue.

Most of the literature has focused on alcohol use disorders. Future studies should also evaluate the impact of psychiatric comorbidity in the treatment outcome of problems related to other drugs.

Key Words: *substance dependence, substance abuse, comorbidity, sex, women, treatment*

Both clinicians and researchers have become progressively more aware of the specific characteristics and distinct treatment needs of women with substance use disorders. According to epidemiologic data, the lifetime prevalence of substance use disorders in North American women is approximately 5% to 8% (1–3). The onset-age of substance use has decreased, and there is evidence for a more marked decrease

among adolescent girls than among boys, potentially leading to an increased risk of progression to substance dependence (4). Women with substance use disorders differ from men with the same diagnosis in various ways. For instance, women are more sensitive than men to the physiological effects of substances. In the case of alcohol, they develop higher plasma concentrations from the same amount of ingested alcohol. The progression from first use to the appearance of substance-related problems and seeking treatment for these problems is significantly faster among women, as is the development of medical consequences of substance use. In addition to the increased morbidity and mortality reported among women with substance use disorders, it has been observed that they are less likely to seek specialized addiction treatment and more likely to seek primary and psychiatric care. Also, addiction in women has a high impact on pregnancy, on the neonate, and ultimately, on the whole family (5,6). Extensive sex differences have also been described in psychiatric comorbidity, with potentially important etiological and treatment implications (7). This article reviews sex differences in psychiatric comorbidity among individuals with substance use disorders and, in particular, the clinical significance of these differences for treatment outcome. The article also critically analyzes the findings.

Method

We performed a computerized search of the literature in English since 1990, using as key words alcohol, drugs, comorbidity, treatment, women, and gender. We examined the following databases: Medline, Psycinfo, CINAHL, Best Evidence, Healthstar, Cochrane Database of Systematic Reviews, and Dissertation Abstracts. To enhance the search, we drew prior relevant articles from the reference lists. We attempted to establish how sex impacts on psychiatric comorbidity, as it relates to treatment and treatment outcome.

Results

Prevalence Rates of Psychiatric Comorbidity With Alcohol Use Disorders

General Population Samples. Using data for the general population between the ages of 15 and 54 years, taken from the US National Comorbidity Survey (NCS), Kessler and colleagues (8) investigated the lifetime co-occurrence of alcohol abuse or dependence with the following lifetime psychiatric conditions: anxiety, mood, drug use, and conduct disorders (CDs); adult antisocial behaviour; and antisocial personality disorder (APD). (Other diagnoses were not included in this analysis.) In this study, women suffering from alcohol abuse presented significantly higher lifetime prevalence of psychiatric comorbidity than did men (72% vs 57%), while the sex difference for alcohol dependence was nonsignificant (86% vs 78%). It was documented that women who abuse alcohol exhibit significantly more anxiety disorders (specifically, social phobia, simple phobia, and posttraumatic stress disorder [PTSD]), mood disorders (specifically, depression and mania), and drug dependence. Conversely, their male counterparts exhibit more antisocial behaviour. It was also observed that women present higher rates of multiple comorbidity (for example, 32% of women in this group had 3 psychiatric diagnoses in addition to alcohol abuse, compared with 14% of men). For alcohol dependence, no significant sex differences in psychiatric comorbidity were described, except for a higher prevalence of drug use disorders among women, compared with men. This last finding seems to be related to the use of tranquilizers by women (9,10).

Helzer and colleagues observe that, in the Epidemiologic Catchment Area Study (ECA) of adults aged 18 years and over, higher rates of psychiatric comorbidity are described for women suffering from either alcohol abuse or alcohol dependence than for men with the same diagnoses (65% vs 44%) (1). For frequent diagnoses, such as major depression and phobic disorders, this finding is associated with higher comorbidity ratios for women than for men (that is, the prevalence in individuals with alcohol use disorders divided by the prevalence in individuals without these diagnoses). Further, diagnoses such as APD, mania, drug use disorders, schizophrenia, and panic disorder also display higher comorbidity ratios in women than in men with alcohol use disorders. Conversely, men with alcohol use disorders present higher comorbidity ratios for obsessive–compulsive disorder (OCD), dysthymia, and cognitive impairment (1).

A recent study of US adults found strong comorbidity between alcohol dependence and pathological gambling, with an odds ratio (OR) of 23.1 (that is, the prevalence in individuals with alcohol dependence divided by the prevalence in individuals without alcohol dependence); however, no sex effect was reported (11).

Comorbidity between alcohol use disorders and PTSD is relevant for women. A community sample of war veterans registered 29% of women with current PTSD and lifetime alcohol abuse (12). Another study of a similar population registered 33% lifetime PTSD and alcohol abuse or dependence (13).

Treatment Samples. Different studies derived from treatment samples have also reported sex differences in psychiatric comorbidity among patients with alcohol use disorders. Psychiatric comorbidity is reported to be higher in women for mood, anxiety, and eating disorders and higher in men for APD (14–19). Comorbid pathological gambling is also reported to be higher in men (20). Women with alcohol use disorders present higher-than-expected rates of bulimia nervosa, but not of anorexia nervosa (21), with the risk being higher when other psychiatric disorders (particularly depression or PTSD) are also present (22,23).

Summary. Both general population and treatment samples show that rates of psychiatric comorbidity are significantly higher for women with alcohol use disorders than for men with alcohol use disorders (except for the nonsignificant higher rates of comorbidity found among women with alcohol dependence in the NCS). Specifically, comorbidity rates are

higher for mood disorders, such as mania and depression, and anxiety disorders, such as phobias and PTSD. Additionally, drug use disorders that are probably associated with tranquilizer use are more frequent among women with alcohol dependence than among men with the same diagnosis.

Prevalence Rates of Psychiatric Comorbidity With Other Drug Use Disorders

General Population Samples. Data from the ECA study show that 76% of men and 65% of women with drug abuse or dependence present at least 1 other lifetime psychiatric diagnosis (including lifetime alcohol abuse or dependence). When one excludes alcohol abuse or dependence, however, the overall psychiatric comorbidity is higher for women than for men. For example, prevalence rates were higher for men regarding comorbid alcohol abuse or dependence and APD, but higher for women regarding comorbid mood disorders (major depression, dysthymia, and mania), anxiety disorders (panic, obsessive–compulsive, and phobic disorders), and schizophrenia (24).

Merikangas and colleagues investigated patterns of psychiatric comorbidity in substance use disorders (including both alcohol and other drugs) (25). These authors combined surveys from Canada, Germany, Mexico, and the Netherlands, in addition to the NCS. Their analysis included mood and anxiety disorders, along with antisocial behaviour and CDs. They observed that overall psychiatric comorbidity was higher for drug use disorders than for alcohol use disorders and that men and women tended to have similar comorbidity patterns. However, in specific sites, women tended to be associated with higher comorbidity rates, particularly where substance use severity levels were lower.

Treatment Samples. Studies of treatment-seeking individuals with cocaine dependence report that women are more likely than men to be diagnosed with depression and phobias, whereas men have higher rates of alcohol dependence, attention-deficit hyperactivity disorder (ADHD), and APDs (26–28).

These results have been confirmed in more recent studies of treatment-seeking individuals with drug dependence (particularly, among those with opiate and cocaine dependence): higher rates of alcohol dependence, APDs, and ADHD have been observed in men (29–31), and higher rates of mood disorders (depression, dysthimia, and mania) and anxiety disorders (phobias, panic disorder, and OCD) have been observed in women (29,30,32). Further, higher rates of psychiatric comorbidity were found in white women, compared with black women, but no similar distinction was found among men in this treatment sample (30). Overall rates of psychiatric comorbidity across sexes range from 47% for current (29) and 73% for lifetime (30) comorbidity, with more lifetime comorbid disorders (excluding alcohol dependence) being identified in women. In treatment settings, women are also reported to present higher rates of comorbid PTSD and cocaine dependence than do men (33). No significant sex differences in comorbidity rates are described for drug dependence and generalized anxiety disorder, schizophrenia, and eating disorders (30).

Conversely, rates of substance use disorders in other psychiatric populations are also high. For example, women seeking treatment for bipolar disorder have rates of substance use disorders 4 to 7 times higher than are found in women from the community (34).

Psychiatric comorbidity is also an issue for nonclinical samples. Among offenders driving while intoxicated, for instance, 50% of women and 33% of men have at least 1 psychiatric diagnosis in addition to substance use disorder—mostly PTSD and depression (35).

Summary. Because alcohol use disorders are so prevalent among men, the resulting comorbidity rates are higher for men than for women with other drug use disorders when these diagnoses are included in rates of psychiatric comorbidity. When only disorders apart from substance use are considered, women present higher comorbidity rates than do men, owing to high rates of mood and anxiety disorders (depression, mania, phobias, and PTSD)—rates similar to reported psychiatric comorbidity in alcohol use disorders but including dysthimia, OCD, and panic disorder. Men, in the other hand, present higher rates of APD and ADHD. Diagnoses such as schizophrenia display inconsistent results, with data from the ECA showing higher rates in women.

Primary vs Secondary Distinction

Most secondary or substance-induced symptoms and disorders will subside with abstinence from substances. However, independent or primary disorders are less likely to improve with abstinence only and require specific attention from clinicians (36,37). The distinction between primary and secondary is reflected in the temporal relation between the disorders' onsets. A causal relation can neither be inferred nor ruled out from the order of onset. In the case of comorbidity with substance use disorders, a psychiatric disorder that has its onset during a prolonged period of abstinence is considered to be an independent disorder requiring integrated management.

Treatment Samples. Studies of sex differences in psychiatric comorbidity show that women who abuse alcohol are more likely than men to have been diagnosed with anxiety and depression prior to the development of the alcohol disorder (38).

Schuckit and colleagues investigated the lifetime prevalence rates for concurrent and independent mood and anxiety disorders in a large sample of alcohol-dependent subjects whose family histories showed high rates of alcoholism and intense rates of inpatient treatment (39,40). Men and women had similar rates of concurrent mood and anxiety disorders, but rates of independent disorders (for example, disorders that began either before the onset of alcohol dependence or persisted during periods of 3 months or more of abstinence) were higher in women than in men. These results are similar to those obtained by Kahler and colleagues. (41).

Compton and colleagues assessed the temporal relation in subjects receiving treatment for drug dependency (mainly, cocaine and opiate addictions) (42). They observed that

women were significantly more likely to have primary generalized anxiety disorders than were men (53% vs 19% respectively), but no other sex distinctions were identified.

General Population Samples. Data from the NCS show that important sex differences emerge in the temporal relation: men are more likely to report their alcohol use disorder as primary, and women are more likely to report it as secondary, to the other comorbid diagnosis. When the alcohol use disorder is secondary, men more often report a prior CD and antisocial behaviour, while women more often report prior mood, anxiety, and drug use disorders (8). In particular, when alcohol use disorders are comorbid with major depression, the ECA study shows that the alcohol use disorder diagnosis is primary in 78% of cases overall. Among women, however, depression predates the onset of alcohol use disorders in 66% of cases (1).

Summary. The evidence suggests that higher proportions of comorbid diagnoses are primary in women with alcohol use disorders, while the opposite is true for men (a higher proportion of comorbid diagnoses are secondary to alcohol use disorders in men). More studies of the temporal relation between the onset-age of comorbid diagnoses and the onset-age of other drug use disorders are needed to clarify whether sex differences (and potentially different treatment needs) also exist in these populations.

Prior Psychiatric Disorder as a Risk Factor for the Onset of Alcohol Use Disorders

Longitudinal data from a 2-year follow-up survey suggest that, for men, depression is not a risk factor for heavy drinking (that is, drinking 5 or more drinks at least once monthly) (43). However, women with depression at baseline display a higher risk for heavy drinking 2 years later, compared with women without depression (43). The NCS shows that the OR of later developing an alcohol use disorder is increased in women with prior depression, compared with men with prior depression (OR 2.26 vs OR 0.32, respectively, for alcohol abuse; OR 4.10 vs OR 2.67, respectively, for alcohol dependence) (8).

Data for subjects with problem drinking were taken from the ECA follow-up study and examined for an association between the occurrence of depression in the previous year and increased drinking in the subsequent year. The association was indeed confirmed, but contrary to expectations, it was found to be stronger in men (44,45).

Regarding prior PTSD, the NCS described no sex difference in the risk of later developing an alcohol use disorder. Women with prior PTSD have a higher risk (OR 3.37) of later developing alcohol dependence, compared with women who do not have PTSD (8). In women, substance use is a risk factor for the development of PTSD following violent assault (46). Alternatively, female crime victims with comorbid PTSD (particularly victims of sexual violence) are more likely to have alcohol and drug problems than are female crime victims without PTSD; thus, PTSD mediates the relation between childhood rape and adult alcohol abuse in women (47). This 2-way relation was further clarified by a 2-year longitudinal study conducted among 3006 American women. The results confirmed the notion of an ever-worsening cycle in which substance use increases the risk of subsequent assault, and assault increases risk of substance use (48).

When sex differences emerged in the NCS regarding other psychiatric disorders, the risk that persons with any or multiple prior lifetime psychiatric diagnoses would later develop alcohol use disorders was found to be significantly higher for women than for men. Specifically, the risk of later developing alcohol abuse was higher in women with a history of social phobia, simple phobia, depression, mania, drug abuse or dependence, and antisocial behaviour than in men with these disorders. Similarly, the risk of later developing alcohol dependence was higher in women with a history of agoraphobia, depression, drug abuse or dependence, antisocial behaviour, and APD than in men with these disorders (8).

Summary. Overall, psychiatric comorbidity represents more of a risk for the development of alcohol use disorders among women than among men. Data from the NCS suggest that depression is a greater risk factor for the development of alcohol abuse or dependence in women than in men, while the ECA suggests that, among individuals with problem drinking, depression is a greater risk factor for subsequent increased drinking for men than it is for women. PTSD is also a risk factor for the development of alcohol use disorders in women, and vice versa, particularly when violence is involved.

Clinical Characteristics of Women With Psychiatric Comorbidity

Because comorbidity between alcohol use disorders and depression is highly prevalent, most of the literature has focused on this topic. Studies have shown sex-specific, genetic, and environmental influences (49), suggesting the potential for etiological implications. Men with comorbid depression and alcoholism present for treatment with more severe alcoholism than do men who have never suffered from depression. Conversely, women with comorbid depression and alcoholism present for treatment with less severe symptoms of alcoholism than are found in women who have never had depression. However, they have more severe depressive symptoms, when compared with their male counterparts. This suggests that the severity of the clinical picture in women with comorbid depression and alcoholism is related mainly to the severity of the depressive symptomatology. Further, women entering treatment without a history of depression present alcohol problems as severe as those presented by men (50).

Recently, Kahler and colleagues reported that the independent or primary depression more often diagnosed in women with alcohol use disorders, compared with men having the same diagnosis, is associated with more dysfunctional attitudes toward oneself and with poorer coping behaviours (41). This observation suggests that such individuals may be particularly vulnerable to recurrent depression.

Compared with substance abusers who do not have comorbid diagnoses, women with comorbid substance abuse and anxiety disorders present a different personality profile, with

lower thrill- and adventure-seeking traits in contrast to their male counterparts (51).

Among persons being treated for cocaine dependence, women represent 48% of those patients diagnosed with comorbid depression, whereas they represent 25% of patients without a diagnosis of depression. These groups have significantly distinct characteristics, with overall worse functioning among patients suffering from comorbid depression and cocaine dependence (52).

An exploratory study among inpatients of a residential program found no significant demographic differences between women and men with comorbid substance use and psychiatric disorders; however, women were more likely to have drug problems in addition to alcohol problems, to have overdosed on drugs, and to report maternal relatives with alcohol and drug problems. Also, women were more troubled by social and family problems requiring counselling and presented for treatment with higher psychiatric severity than did men (53).

Some studies (54,55), but not all (53), have also described more severe medical problems in women with comorbid substance use and other psychiatric diagnoses than in men with these diagnoses.

Women with substance use disorders combine 2 important risk factors for both suicidal ideation and suicide attempt, the risk being 1.7 to 2.2 times higher in women than in men and 3.9 to 5.8 times higher in persons with substance use disorders than in those without such a history. Psychiatric comorbidity poses additional risk for suicidal behaviour in women with multiple comorbidity (56). Clinical studies also show that women with substance dependence report suicide attempts more often than do men with the same diagnosis (57).

Summary. Psychiatric comorbidity is associated with distinct clinical presentations according to sex (particularly in terms of each disorder's severity), of overall functioning, and of suicide risk profiles. The severity of the clinical picture in alcohol use disorders is to a greater extent owing to depression in women with comorbidity and to a greater extent owing to the alcohol disorder in men with comorbidity.

Psychiatric Comorbidity as Predictor of Treatment Outcome

Even though extensive literature documents the high prevalence of depression in substance use disorders, particularly in women, only a few studies address the impact of this comorbidity on outcome. Several studies from the 1970s and 1980s observe that treatment outcome for alcoholism is worse for men with comorbid depression and alcoholism, compared with the outcome for men without comorbidity, while the opposite is true for women (16,58–60). This differential outcome seems to be associated with a lifetime diagnosis of depression and shorter follow-ups. With longer follow-ups, the sex difference in treatment outcome tends to disappear, with overall better outcomes at a 3-year follow-up for both women and men with lifetime comorbid depression than for those without comorbidity (61). Again, no sex difference in the effect of depression on drinking outcome was found at a 1-year follow-up when current, rather than lifetime, depression was taken into account, but the drinking outcome was worse when depression was present. In the same study, however, the prescription of antidepressants for subjects with comorbidity was associated with longer time to relapse (62). Similarly, in a 5-year follow-up study, improved depression symptoms in subjects with comorbidity was significantly related to better treatment outcome for alcohol use, with no sex differences (63). Further, the temporal relation of depression and substance use disorders likely affects substance use treatment outcomes (64). (The results of this study were not reported by sex.) Finally, Hodgins and others found that women with alcohol dependency and a diagnosis of major depression at some time within their lifetime were significantly more likely to have primary depression, compared with their male counterparts (69% vs 35% respectively) (65). Men, however, were more likely to suffer from current depression than were women (29% vs 10%). This 3-year follow-up study did not identify any sex differences in the effect of depression on alcohol drinking outcome. Given the inconsistency of the results, it is clear that a better understanding of the impact of sex on the comorbidity of substance use disorders and depression and the relation of sex to treatment outcome is still much needed. Key variables need to be further defined so that findings can be compared. They include the nature of depression diagnosed (lifetime or current and primary or secondary), whether and how depression was addressed, and time of follow-up (short- or long-term).

The impact of other comorbid psychiatric disorders on the treatment outcome for substance use disorders has been less studied, and the role of sex needs further investigation. For example, although the comorbidity between cocaine dependence and depression has been studied for its treatment impact, and depression in subjects who abuse cocaine has been associated with both better (66) and worse (67) retention and abstinence outcomes, sex differences were not analyzed.

Summary. Not all studies identify sex differences in the treatment outcome of individuals with comorbid alcohol use disorders and depression. However, some evidence suggests that lifetime diagnosis of depression is associated with better short-term prognosis for the alcohol disorder in women, as opposed to men. Further, current depression per se is associated with poorer prognosis for the alcohol disorder, regardless of sex. However, antidepressant treatment may be associated with better outcome for problem drinking.

Treatment of Women With Comorbid Substance Use Disorders

Sex differences in the response to several medications have been reported, attributable at least in part to differing pharmacokinetics between the sexes. For example, women with depression seem to respond better to selective serotonin reuptake inhibitors (SSRIs), while men with depression seem to respond better to tricyclic antidepressants (TCAs) (68). Variability by sex has been reported in regard to the potential of some SSRIs to reduce alcohol consumption (69). However, most efficacy studies investigating pharmacotherapy

treatment of individuals with alcohol use disorders have failed to analyze data by sex. For instance, Naranjo and others observed that, among individuals with alcohol dependence but without depression, men benefited more than women from citalopram treatment, reinforcing the importance of considering sex in the analysis (70). Other authors have provided preliminary evidence regarding the efficacy of fluoxetine in the treatment of patients with comorbid alcohol dependence and severe major depression, but sex differences were not investigated (71).

There is some evidence showing that, among individuals with alcoholism, a negative mood (not necessarily major depression) influences craving for alcohol in distinct ways according to sex, being associated with increased alcohol craving in women but not in men (72). This finding suggests that mood may be an important determinant in relapse for women with alcohol use disorders and underscores the need to develop specific relapse-prevention strategies focusing on coping skills for depression.

Psychotherapeutic trials analyzing sex differences are also needed. A large, 8-year clinical trial designed to investigate whether individuals with alcohol use disorders responded differently to specific psychotherapeutic approaches reported that, compared with men, women generally presented better outcomes following hospitalization; however, no sex effect in treatment matching was found (73). Specific treatments for individuals with psychiatric comorbidities were not investigated.

Recurrent depressive episodes and suicidal ideation in women with substance use disorders are often part of a broader picture compatible with a diagnosis of borderline personality disorder (BPD). Dialectical behaviour therapy is a specific type of time-limited, cognitive-behavioural approach that combines individual psychotherapy with skills training focusing on emotion-regulation and acceptance strategies. It was developed to treat chronically suicidal women with BPD. Preliminary data for women with comorbid substance dependence and BPD suggest that, compared with traditional treatments in the community, this approach is associated with greater reductions in substance use and improved overall functioning, as well as with increased treatment retention (74,75). It has been further suggested that women with substance use disorders and a history of trauma may benefit from psychodrama strategies, but specific research is still lacking (76).

Summary. There is some preliminary evidence that sex differences may exist in the pharmacologic treatment response of individuals with alcohol use disorders. To our knowledge, however, no studies have investigated differential responses to pharmacotherapy in individuals with comorbid conditions. Further, the importance of a depressive mood in relapse for women with alcohol use disorders has been recognized, and some preliminary data point out the efficacy of specific psychotherapeutic interventions for women with comorbid conditions, but additional research efforts are clearly needed.

Discussion

Generally, more recent cohorts confirm earlier study results indicating sex differences in the prevalence rates of psychiatric comorbidity among individuals with substance use disorders. In most studies, overall rates are consistently higher for women than for men. One possible explanation is that, because substance use is less normative for women than for men (that is, less socially acceptable for women), those women who develop a substance use disorder may represent a more severely afflicted population at higher risk for psychiatric comorbidity. An alternate explanation is that women with psychiatric disorders are more likely than men to use substances to self-medicate and are therefore at higher risk for developing secondary substance use disorders. Further research is needed to confirm or refute these hypotheses. Sex differences in the rates of specific disorders were also consistently observed: in particular, higher rates of depressive and anxiety disorders were observed in women, and higher rates of substance use disorders and APD were observed in men. This distribution does not simply reflect the general population pattern: these estimates are also based on ORs or prevalence ratios (that is, the risk and prevalence rates of a psychiatric disorder in individuals with a substance use disorder relative to the rates of a psychiatric disorder in individuals without a substance use disorder). Thus, these rates indicate that individuals with substance use disorders display relative increases in specific psychiatric disorders, compared with the general population. The use of odds or prevalence ratios may also explain the NCS findings: in that study, the sex difference for psychiatric comorbidity among individuals with alcohol use disorders was significant only for alcohol abuse but not for alcohol dependence. For instance, although 48.5% of women with a lifetime diagnosis of alcohol dependence also fulfilled criteria for depression, compared with only 24.3% of men with the same diagnosis, the sex difference in the OR is nonsignificant. These differential results regarding alcohol abuse and alcohol dependence suggest that the sex difference in psychiatric comorbidity may be more subtle at higher levels of alcohol use severity (alcohol dependence) than at lower levels (alcohol abuse). Care must be exercised when analyzing prevalence rates, since large differences emerge when one considers treatment, as opposed to epidemiological, samples and inpatient, as opposed to outpatient, samples, as well as lifetime, as opposed to current, diagnosis. The attempt to generalize results derived from treatment samples is complicated by the fact that their subjects often represent the more severe end of the spectrum of substance use disorders. Some studies looking at Axis I comorbidity rates in subjects dependent on other drugs include alcohol use disorders, and others do not. Other common comorbid conditions, such as pathological gambling, eating disorders, ADHD, and personality disorders other than APD are usually not included. Selectively including some diagnoses but not others may bias the results. Particularly for personality disorders, including only the antisocial subtype in most surveys usually yields higher rates of personality disorders for men. Including other personality disorders may reveal important sex differences in Axis II

comorbidity. These differences in diagnostic inclusion and definition may at least partly explain discrepancies among prevalence studies.

It is clinically significant that individuals presenting for treatment with a comorbid substance dependence and psychiatric disorder show significant sex differences in the severity of both conditions, as well as in overall functioning. In particular, clinicians need to deal with the substantially higher risk of suicide attempts that women with comorbid diagnoses display, compared with men. Close monitoring is relevant, especially when one considers that women with substance use disorders are more likely to have a partner suffering from addiction than are men; consequently, they have less spousal support to encourage treatment and follow-up. As well, communication among health professionals is essential, because women with comorbid conditions may have more severe physical conditions than men and are more likely to be prescribed potentially addictive medications, such as tranquilizers, sleeping pills, and analgesics. This puts them at greater risk for iatrogenic dependencies and doctor-shopping behaviour. Women with primary or independent mood or anxiety disorders in addition to substance disorders may need long-term follow up. Further, they should be taught to monitor potential symptoms of recurrence, so that they may recognize them early and forestall a subsequent relapse of their substance use disorder.

It is also clear that the literature focusing on alcohol use is somewhat more developed than is research on other drugs. Some of the sex differences in psychiatric comorbidity described for individuals with alcohol use disorders may also apply to individuals with other drug use disorders. Further studies are needed to confirm this trend.

The distinction between primary and secondary depression is particularly helpful for women with substance use disorders; they will more frequently display a primary or independent disorder potentially requiring specific antidepressant treatment. Some authors recommend that, ideally, clinicians wait until the patient has had 3 to 4 weeks of abstinence before establishing an independent diagnosis of depression (36). However, a careful history may reveal the presence of a clearly primary depressive disorder, favouring more immediate treatment. The intensity of depressive symptoms may seriously impair a patient's ability to achieve abstinence. In these circumstances, treating depression with antidepressants needs to be considered even when complete abstinence has not been reached, because treatment is often associated with subsequently reduced quantity and frequency of drinking. Antidepressants may also be indicated for patients with comorbidity who have a chronic course, with depressive symptoms persisting during past attempts at abstinence, or who have a family history of mood disorders (77). To avoid cycling secondary to antidepressants, it is also important to determine whether a depressive disorder is unipolar or bipolar. Several medications are metabolized by the liver, and monitoring liver function is essential, because women with alcohol dependency develop alcohol-related liver impairment faster than men, with less total alcohol consumed (6). Because a depressive episode represents a risk factor for later development of alcohol use disorders in women, and because women have a higher risk for progressing to a chronic course, we recommend early screening for, and vigorous treatment of, depression in women.

The extent to which these principles should apply to other psychiatric diagnoses in comorbidity with substance use disorders is uncertain, but it is likely, for example, that the same rationale could be considered for anxiety disorders. For disorders such as pathological gambling, schizophrenia, and eating disorders, concurrent treatment is indicated whether or not the disorder is primary. More research is needed to clarify and develop this aspect of comorbid treatment and to establish monitoring and safety guidelines. Likewise, studies to develop related specific psychotherapeutic and relapse prevention interventions are much needed.

Because psychiatric disorders, particularly depression and PTSD, are associated in women with increased risk for developing substance use disorders, careful psychiatric assessment and treatment of these conditions may prevent the occurrence of substance use disorders.

Finally, psychiatric comorbidity affects treatment outcome in distinct ways according to sex. At least for the comorbidity between depression and alcohol use disorders, the prognosis for women with comorbidity is better than that for their counterparts without comorbidity, while the opposite seems to be true for men. Again, further studies are needed to clarify the nature of this relation; the difference was found in the short-term follow up but disappeared in the longer term. Last, it is not totally clear how lifetime and current diagnoses influence treatment outcome, but evidence confirms that the adequate management of comorbid depression improves treatment outcome for substance use disorders, particularly among women.

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Résumé: Troubles liés à l'utilisation d'une substance : différences selon le sexe et comorbidités psychiatriques

Objective : Cet article étudie les différences selon le sexe de la comorbidité psychiatrique chez les personnes souffrant de troubles liés à l'utilisation d'une substance et en particulier, la signification clinique de ces différences en ce qui concerne le résultat du traitement chez les femmes.

Méthode : Nous avons entrepris une recherche informatique des principales bases de données sur la santé. Pour améliorer la recherche, nous avons prélevé des articles pertinents dans les listes bibliographiques.

Résultats : Les femmes ayant des troubles d'alcoolisme ou d'autre drogue présentent des taux plus élevés que les hommes de comorbidité psychiatrique, en particulier des troubles anxieux et de l'humeur. En outre, le diagnostic comorbide, surtout de la dépression, est plus souvent primaire chez les femmes, alors que chez les hommes, la comorbidité est plus souvent consécutive au diagnostic d'abus de substance. De plus, il a été prouvé que la comorbidité psychiatrique est associée à des résultats distincts, selon le sexe, du traitement de la toxicomanie.

Conclusions : Les différences selon le sexe de la présentation clinique des personnes dépendantes de substances ayant une comorbidité psychiatrique représentent des défis et des possibilités spécifiques pour le traitement.