Severe alcohol use disorder after initiation of selective serotonin reuptake inhibitor therapy

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A 52-year-old woman was admitted to a facility for assistance with alcohol withdrawal. She described symptoms of severe cravings, involving a 6-month period of escalating alcohol use. She received a diagnosis of severe alcohol use disorder (AUD) meeting all 11 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for AUD. Her alcohol use had increased from approximately a half bottle of wine daily (about 2.6 Canadian standard drinks[1]) in the evening at baseline, to morning alcohol use and a total of approximately 2 bottles of wine, plus additional spirits (about 18 standard drinks) daily.

She reported that before the emergence of severe AUD, she was employed, married and stably housed. She stated that her long-standing baseline use was associated with working in an industry where socializing with alcohol was common. However, she did not think that alcohol had previously caused meaningful problems in her life, and she did not have earlier prolonged periods of low mood. She described experiencing hangovers and weight gain possibly from alcohol, consistent with a mild AUD, although it was uncertain whether she met the DSM-5 threshold of "clinically significant impairment or distress" secondary to her alcohol use.

She reported increasing anxiety and depressive symptoms, which she associated with social isolation during the COVID-19 pandemic. She saw her family physician, who prescribed escitalopram for depression. Escitalopram was titrated from 5 mg per day to 20 mg per day, and she remained on the medication for 6 months without improvement of mood symptoms. Coinciding with initiation of escitalopram, she reported increasing cravings and compulsion to use alcohol, such that she began drinking in the morning and throughout the day, as described on admission to the medical withdrawal facility.

Because the patient had not derived depressive symptom improvement from the selective serotonin reuptake inhibitor (SSRI) therapy, and in light of her increasing craving symptoms and increased alcohol use, the treating addiction physician recommended a taper of her prescribed escitalopram over a 3-week period upon completion of alcohol withdrawal management. She was prescribed naltrexone, an alcohol anticraving medication. The patient took the naltrexone but elected to discontinue it after the SSRI taper was completed, because her alcohol craving symptoms had resolved. Six months after withdrawal management and cessation of SSRI therapy, she remained abstinent from alcohol and free of depressive symptoms.

Key points

- Antidepressants of the selective serotonin reuptake inhibitor (SSRI) class are commonly prescribed in Canada, including to people with, and at risk of, alcohol use disorders (AUDs).
- Meta-analyses suggest that depressive symptoms may not improve with SSRI therapy in people with concurrent AUD.
- Clinicians should offer treatment of underlying AUD with first-line pharmacologic (e.g., naltrexone) and behavioural interventions.
- Clinicians should also be aware that some patients may develop AUD or have their AUD aggravated by SSRIs.

Discussion

Alcohol is used by about 75% of the population in Canada and is a major cause of preventable disease, injury and death.[1] In 2017 alone, alcohol was implicated in 18 000 deaths and cost Canadian health systems $5.4 billion.[1] Almost 20% of people in Canada meet the criteria for AUD during their lifetime.[2]

Common comorbidities presenting with AUD include depression and anxiety. It is estimated that the lifetime prevalence of substance-induced depression in people with AUD is 26%, while 15% have at least 1 major depressive episode.[3] Although anxious and depressive symptoms are often experienced because of social harms of AUD, some symptoms may also be a manifestation of neurological processes, including adrenergic withdrawal symptoms experienced as anxiety. Because AUD may present with symptoms such as insomnia, dysphoria or anxiety (including circumstances in which patients may not be aware of the contribution of alcohol), clinicians may treat mental health symptoms rather than address the root issue of excessive alcohol use.[4] Indeed, substance-induced depression, anxiety and insomnia typically resolve rapidly with cessation of alcohol.[4]

This patient's case was complex and involved a number of confounding social circumstances, such as the COVID-19 pandemic and increasing isolation. Although the initiation of an SSRI appeared to be a likely explanation for the escalation in this patient's alcohol use, other factors may also have played an important role. This case illustrates that although it may be common practice to prescribe SSRIs for people with AUD,[2,4] SSRIs may not be effective for depressive symptoms in people with concurrent AUD, and may worsen alcohol use in some.

Research suggests that depressive symptoms may not improve with the use of SSRIs in people with active AUD. A 2018 systematic review comparing antidepressants to placebo in people with co-occurring depression and alcohol dependence found no statistically significant reduction in the severity of depressive symptoms when studies at high risk of bias were removed.[5] The authors of the review acknowledged that a major limitation to the research in this area is the difficulty of diagnosing a primary mood disorder in a person with AUD.[6] A meta-analysis seeking to differentiate substance-induced or undifferentiated depression versus major depressive disorder (MDD) in people with AUD found that SSRIs significantly, albeit modestly, reduced depressive symptoms in the MDD group, but not in the group with substance-induced depression.[7] However, a 2020 meta-analysis that was restricted to studies in which MDD and AUD were documented did not support the benefit of SSRIs in this population, concluding that "SSRI-based treatments had no effect" on MDD in people with AUD.[6] Importantly, most of these studies included only participants who were actively drinking, and therefore cannot be applied to people who are in sustained remission from AUD.

Taking a thorough history of substance use and documenting baseline substance use is important when assessing a person with depressive symptoms. Clinicians may attempt to differentiate substance-induced depression from MDD by assessing whether the history of depressive symptoms started before the onset of substance use, or depressive symptoms occurred during periods of sustained abstinence (≥ 6 wk is ideal).[3,4] The new Canadian guideline on the treatment of AUD recommends treating underlying AUD with first-line pharmacologic (e.g., naltrexone) and psychosocial treatments, and behavioural interventions such as cognitive behavioural therapy are recommended for concurrent depressive symptoms.[8] There is less robust evidence examining other pharmacotherapy for depressive symptoms in people with AUD; however, some studies suggest that non-SSRI antidepressants may have benefit.[6,9]

The impact of SSRI treatment on drinking outcomes in people with AUD has also been the subject of research. A systematic review of randomized controlled trials (RCTs) found improvement in some alcohol-related outcomes with the use of SSRIs (number of participants abstinent, number of drinks consumed per day) but no clear improvement in other outcomes such as rate of abstinent days, number of people who drink heavily, and time before first relapse.[5] A more recent meta-analysis found no benefit of SSRIs on alcohol abstinence in this population.[6] In addition, a series of RCTs and a case series of 93 patients suggest that a subgroup may have worsening alcohol-related outcomes when prescribed SSRIs.[10–13] The mechanism underlying any worsening alcohol use remains unclear, but increased cravings have been reported.[10] Disinhibition and increased impulsivity have also been proposed[4] and may be mediated by increased dopamine release in the nucleus accumbens.[13]

In an RCT involving 265 patients with AUD, the treatment group receiving an SSRI had worsening symptoms of AUD, including increased days drinking, increased number of drinks per drinking day, and increased amount of money spent on alcohol.[11] Although not consistently reported, other RCTs suggest that in people who initiate alcohol use at a younger age and have more severe AUD, alcohol use may increase as a result of SSRI therapy, whereas SSRI therapy in those with later-onset and less severe AUD may lead to reduced alcohol use.[12,14] Investigators have suggested that the 5-hydroxytryptamine transporter–linked promoter region genotype may be responsible for this phenomenon.[14] At present, however, the evidence is inconclusive and there is no "test" that might help guide clinicians in determining who may be at increased risk of this adverse outcome. Of additional relevance — given that people who use alcohol commonly use other substances — some studies of SSRIs or serotonin and norepinephrine reuptake inhibitors in other substance use disorders have similarly reported worsening of substance use outcomes without benefit to mental health symptoms.[6,15]

Evidence-based interventions to support the mental health of people who use alcohol remain an urgent priority, along with more high-quality research in this area. The case of this patient emphasizes the need to thoroughly consider an individual patient's circumstances and complexity before initiating SSRIs, including taking a careful history of substance use with documentation of baseline levels of substance use. It is reasonable to continue SSRIs in people with AUD whose depressive symptoms have improved as a result of this treatment and whose alcohol use has not worsened. However, as with any other medication class, patients whose symptoms do not improve with SSRI therapy should have their medications reviewed as part of usual care. Additionally, adverse reactions cannot always be foreseen, and clinicians should be alert to patients experiencing increased substance use that coincides with initiation of SSRI therapy, and discontinue as appropriate.

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