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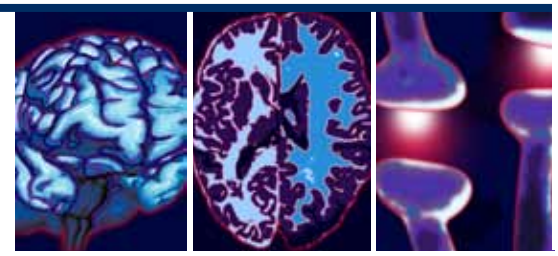

Clinical implications of alcohol-use disorders in schizophrenia

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Practice points

- The clinical course of schizophrenia can be characterized by four stages: a premorbid stage often recognized in individuals with family histories of the disorder, a prodromal stage where subclinical symptoms are first expressed, the first episode of schizophrenia when psychosis first appears in its full form and a maintenance stage of schizophrenia when there may be active or residual psychotic symptoms.
- Each stage of the clinical course of schizophrenia is characterized by elevated rates of alcohol-use disorders (AUDs).
- AUDs in this clinical population may be linked to neurobiological abnormalities within the reward system that may have functional implications for both addiction and schizophrenia.
- AUDs in this clinical population may also be linked with personality characteristics that predispose them to be sensitive to stress, to use ineffective coping skills, and to turn to alcohol to relieve dysphoria.
- Research on AUDs in the first two stages, although minimal, suggests that prodromal individuals with AUDs are at risk for increases in perceptual abnormalities and strange behaviors.
- Research on AUDs in the latter two stages of schizophrenia suggests that AUDs are associated with exacerbated psychopathology, medication noncompliance, cognitive dysfunction, poor community functioning and poor physical health outcomes.
- The design of interventions for premorbid and prodromal individuals would benefit from considering the evidence-based implications of alcohol at these specific stages of the disorder.
- Naltrexone and disulfirate currently have US FDA approval as treatments for AUDs, and have shown some efficacy in individuals with schizophrenia. However, the use of these drugs has not yet been evaluated at all stages of the disorder.

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Future Medicine part of fsg

Practice points (cont.)

- Interventions integrating psychopharmacology with psychosocial treatment would offer new hope to reduce alcohol use and improve long-term outcomes in individuals with schizophrenia.

SUMMARY Evidence suggests that there are elevated rates of alcohol-use disorders (AUDs) at each stage of schizophrenia. Although the literature examining the clinical implications of alcohol at the early stages of schizophrenia are rather sparse, findings from numerous studies suggest that comorbid AUDs in individuals with schizophrenia exacerbate psychopathology, undermine medication compliance, add to cognitive dysfunction, impaired community functioning and physical health. Although there are several clinical implications of AUDs, their inter-relationships are not well known and must be further studied to present a clearer clinical picture. Gaps in the literature and areas for future research will be discussed.

The clinical course of schizophrenia suggests that the disorder can be characterized by four stages [1]. The premorbid stage occurs before any of the psychotic features of the disorder emerge and is best recognized by studying individuals with family histories of the disorder (i.e., familial high-risk [FHR] individuals). A wealth of evidence suggests that FHR individuals are characterized by cognitive impairment and neurobiological abnormalities [2–5]. The prodromal stage begins with a period of decline in everyday functioning and intermittent changes in behavior prior to the first appearance of psychosis [6]. Several studies suggest that the prodromal stage is accompanied by progression of attenuated symptoms in FHR individuals [7,8] and loss of cortical gray matter [9–11].

The first psychotic episode of schizophrenia (FES) stage begins with the first full appearance of psychotic symptoms (e.g., hallucinations and delusions), and again, during this stage, there is evidence of further cognitive impairment [12,13] and cortical gray matter loss [9,14,15]. Finally, the maintenance stage of schizophrenia is highly variable, and to a great extent, depends on the response of the individual with schizophrenia to treatment. During the maintenance phase, there may be persistent psychotic symptoms, as well as increasing negative symptoms and thought disorganization. Cognitive deficits also persist during this phase although their severity tends to stabilize [16,17]. This stage is also characterized by a host of neurobiological abnormalities that have progressed since the first psychotic episode [18] and continue to progress throughout the duration of the illness [19].

The clinical presentation of schizophrenia is also frequently characterized by the presence of comorbid alcohol-use disorders (AUDs). A recent meta-analysis suggests the mean lifetime AUD prevalence rate for individuals during FES or the maintenance phase of the disorder is a concerning 23.4% [20]. However, some studies have found this rate to be even higher, ranging between 43.1 and 65% [21–23]. Furthermore, known risk factors for a comorbid AUD among individuals with schizophrenia include low educational attainment, a family history of AUDs, and prior violent offenses [24].

Research investigating clinical populations suggests that alcohol is used during times of distress, when individuals are unable to use adaptive coping strategies to deal with negative events [25,26]. For individuals with schizophrenia, the use of alcohol can become a common means to regulate or cope with a distressful affective state [27–30] as they tend to lack the necessary problem-solving skills and strategies to successfully cope with stress [31,32]. Blanchard and colleagues suggested that substance-use disorders (SUDs) associated with schizophrenia can be explained by an affect regulation model, where individuals with schizophrenia have anxious personalities that are especially vulnerable to stress. Thus, patients are unable to initiate effective problem solving and coping skills to alleviate negative affective states during stressful situations and turn to alcohol as a mechanism for coping [33].

Alcohol has intoxicating effects that range from sedation to elation [34], and individuals at risk for AUDs may be more sensitive to the elating effects of alcohol [35]. In other words, it is the rewarding rather than sedating effects of alcohol that promote abuse and dependence [36]. Consistent with the hypothesis that individuals with schizophrenia are vulnerable to AUDs,

D'Souza and colleagues found that individuals with schizophrenia reported heightened euphoric and stimulating effects of alcohol when compared with controls [37]. This enhanced sensitivity to alcohol for individuals with schizophrenia could be associated with abnormalities in the brain's reward system, which have been linked to the neurobiology of both addiction and schizophrenia [38,39]. Furthermore, comorbid AUDs have been associated with increased cognitive impairment and psychopathology [37,40], and an exacerbation of neuroanatomical abnormalities among individuals with schizophrenia [40–42].

Although the clinical implications of SUDs in schizophrenia have previously been reviewed [30,43,44], we focus on the clinical implications of co-occurring AUDs within each of the four stages of schizophrenia. Specifically, we will report the AUD prevalence rate at each stage and examine the impact of AUDs on the clinical features of patients within each of these stages. Although research suggests individuals with schizophrenia have elevated lifetime prevalences of abuse or dependence on multiple substances [45], we focused on alcohol as it is the most commonly used substance among individuals with schizophrenia [46] that influences psychopathology [47] and has long-term implications for chronic health conditions [48,49].

We conducted an exhaustive search on PubMed, Google Scholar, PsychInfo and Web of Knowledge for literature discussing the clinical implications of AUDs in schizophrenia. The following key words were included in our search using various permutations: 'alcohol', 'substance use', 'schizophrenia', 'psychosis', 'premorbid', 'FHR', 'prodromal', 'first episode', 'comorbid', 'dual diagnosis', 'psychopathology', 'medication' 'compliance', 'hospitalization', 'cognition', 'medication compliance', 'function' and 'physical health'. Once articles were identified, we then reviewed them to identify which studies reported clinical implications related to alcohol.

Premorbid stage of schizophrenia

There have only been two studies on the rate of an AUDs (i.e., abuse or dependence) among individuals who are at FHR for schizophrenia. The first study examined nonpsychotic siblings of individuals with schizophrenia, and determined that 43.4% of these individuals (mean age: 23.1 years [standard deviation = 3.8]) received a research diagnosis of a lifetime AUD [21]. In addition, the North American Prodromal Longitudinal Study found that 5.1% of FHR individuals (n = 39, mean age: 19.4 years [standard deviation = not reported]) had an AUD [50]. The discrepancy between these prevalence rates may be explained by the difference in the mean ages of these groups, as well as the fact that early psychotic symptoms were also present in the individuals who participated in the latter study.

In a retrospective assessment of individuals with schizophrenia who had already experienced their first psychotic episode, Compton and colleagues found that individuals who progressed from 'non-use' or 'having ever used alcohol' to 'weekly alcohol use' were more likely to also experience the onset of prodromal symptoms [51]. Welch and colleagues examined the neuroanatomical characteristics of FHR individuals, some of whom subsequently developed schizophrenia. They found that alcohol use exceeding safe limits was associated with reduced gray matter volume and increased ventricular volume, and that FHR individuals with alcohol dependence were more likely to develop the full-blown form of schizophrenia [52]. Thus, the use of alcohol in FHR individuals appears to interact with other susceptibility factors to increase the likelihood that they will progress to develop more advanced stages of the disorder.

Although a few studies suggest that individuals with FHR may have elevated AUD rates, further research is needed to advance these findings and answer several remaining questions, including whether or not there is an increased risk of AUDs in FHR individuals? Does the presence of an AUD increase the risk for psychosis or other psychiatric disorders? Do neuroanatomical abnormalities compounded by AUDs increase the risk for psychosis? Research will also be needed to examine the clinical implications of AUDs in this group, including the impact on subclinical psychopathology, cognition, community functioning and physical health. By examining the clinical implications of AUDs, research has the opportunity to shed light on whether FHR individuals have additional vulnerabilities that could be exacerbated by having AUDs. In turn, interventions can be designed to address these alcohol-related issues and attempt to prevent the onset of psychosis or other psychiatric disorders. Key characteristics of the studies reviewed in this section are presented in **Table 1**.

Table 1. Factors associated with alcohol-use disorders during the premorbid risk stage of schizophrenia.

Study (year)	Sample	Major findings	Ref.
Compton *et al.* (2009)	n = 109 first episode SCZ (mean age: 23.1 years; SD: 4.7)	Progression from 'non use' or 'having ever used alcohol' to 'weekly use' contributed to the onset of prodromal symptoms	[51]
Smith *et al.* (2008)	n = 53 nonpsychotic siblings of SCZ (mean age: 23.1 years; SD: 3.8); n = 59 SCZ (mean age: 23.5 years; SD: 3.2); n = 80 CON (mean age: 21.2 years; SD: 3.5); n = 75 siblings of CON (mean age: 21.3 years; SD: 3.5)	43.4% of nonpsychotic siblings had a lifetime history of an AUD. Nonpsychotic siblings had a fourfold risk of an AUD (OR: 4.0), over the comparison group, after covarying for age and gender	[21]
Welch *et al.* (2011)	n = 147 FHR individuals; n = 36 CON; 16–25 years old	Moderate-to-high levels of alcohol use were correlated with an increase in ventricular size. Alcohol dependence was associated with subsequent development of schizophrenia	[52]
Woods *et al.* (2009)	n = 40 FHR individuals (mean age: 19.4 years); n = 377 prodromal individuals (mean age: 18.2 years); n = 198 help-seeking CON (mean age: 16.1 years); n = 49 schizotypal personality disorder (mean age: 16.1 years); n = 196 CON (mean age: 18.7 years); age SDs not reported	5.1% of FHR individuals had a lifetime history of an AUD	[50]

AUD: Alcohol-use disorder; CON: Control subjects; FHR: Familial high risk for schizophrenia; OR: Odds ratio; SCZ: Individuals with schizophrenia; SD: Standard deviation.

Prodromal stage of schizophrenia

The prodromal stage of schizophrenia is defined by attenuated positive symptoms as assessed using the Structured Interview for Prodromal Symptoms (SIPS) [53]. In a population of several hundred prodromal individuals, 13.6% had a lifetime AUD diagnosis [50]. Other studies have found that the lifetime AUD rate during the prodromal stage ranges from 8–28% [54–56]. The presence of AUDs in prodromal participants has been correlated with subclinical positive symptoms and thought disorganization [55], while higher rates of conversion from the prodromal stage of schizophrenia to the first episode of schizophrenia stage has been associated more broadly with SUDs [57]. However, more research is needed to examine whether AUDs uniquely contribute to an increased conversion rate from the prodromal stage to a first episode of psychosis, or other psychiatric disorders.

If the presence of AUDs at this stage are associated with conversion to an axis I psychiatric disorder, the need to intervene is heightened in order to reduce this additional risk. Thus, longitudinal studies of the prodrome have the opportunity to study this relationship and provide evidence to support whether or not alcohol is a unique risk factor for conversion. Further, AUDs may also contribute to exacerbated cognitive impairment, difficulties with community functioning and physical-health outcomes. By identifying whether there are additional vulnerabilities associated with AUDs among prodromal individuals, interventions can be designed to target treatment and prevention of AUDs in this at-risk group. Key characteristics of the studies reviewed in this section are presented in Table 2.

First psychotic episode of schizophrenia

The FES is characterized by an initial full-blown appearance of psychotic symptoms and the subsequent 3-year period [1]. Several studies report that AUDs are prominent during this phase of schizophrenia with a prevalence rate of 24–43% [58–63]. A recent meta-analysis reported that the AUD prevalence rate during this stage does not differ from the prevalence rate during the maintenance stage [20].

■ Psychopathology

The literature indicates that comorbid AUDs influence the severity of psychopathology in first-episode patients. Most [59,60,64], but not all [62] studies suggest that FES individuals with a comorbid AUD had more severe hallucinations, delusions and perceptual abnormalities. Other studies found that FES individuals with SUDs were more likely to relapse after their symptoms remitted [61,65]. However, whether AUDs uniquely contribute to this elevated risk of relapse is not yet known. Thus, additional research is needed to investigate whether AUDs uniquely contribute to relapse among FES individuals.

Table 2. Factors associated with alcohol-use disorders during the prodromal stage of schizophrenia.

Study (year)	Sample	Major findings	Ref.
Cannon *et al.* (2008)	n = 291 prodromal individuals (mean age: 18.1 years; SD: 4.6)	A history of substance abuse (but no individual substances) was a significant predictor of transition from the prodrome to psychosis	[57]
Korkeila *et al.* (2005)	n = 39 prodromal individuals, n = 17 subjects with minor symptoms, and n = 77 comparison subjects with no prodromal symptoms (mean age: 33 years; SD: not reported)	28% of prodromal individuals had alcohol abuse. Alcohol abuse was significantly correlated with positive symptoms	[55]
Marshall *et al.* (2011)	n = 48 prodromal individuals (mean age: 21.1 years; SD: 4.2)	8% of prodromal individuals had a lifetime AUD	[54]
Rosen *et al.* (2006)	n = 29 prodromal individuals (mean age: 18.4 years; SD: 4.8), n = 29 nonprodromal individuals (mean age: 19.2 years; SD: 6.4)	21% of prodromal individuals had a current alcohol-use disorder; 28% of prodromal individuals had a lifetime AUD	[56]
Woods *et al.* (2009)	See Table 1	13.6% of prodromal individuals had a lifetime AUD	[50]

AUD: Alcohol-use disorder; SD: Standard deviation.

■ Medication compliance & hospitalization

Although co-occurring SUDs contribute to medication noncompliance and hospitalization [61,65], the relationship between comorbid AUDs and medication noncompliance among FES individuals remains unclear. While some studies suggest that AUDs are associated with medication noncompliance in FES individuals [63,66], other studies report that there is no relationship [60,67]. Future research could help clarify this relationship by examining whether AUDs have an indirect effect on medication noncompliance in FES individuals by compounding the side effects of antipsychotic medication, which have been associated with medication noncompliance [68]. As such, exacerbated side effects could influence noncompliance, and subsequently increase the risk of relapse. Treatment compliance is critical at this early stage, and services would be better equipped to understand the impact of AUDs on treatment adherence. Interestingly, AUDs were not identified as risk factors for hospitalization [69,70] or length of hospitalization [64].

■ Cognition & community functioning

AUDs are known to impair cognitive functioning [71], and thus, we would expect that comorbid AUDs would exacerbate cognitive impairment in schizophrenia. However, in one study where FES individuals with and without comorbid AUDs were compared, the severity of cognitive impairment did not differ between groups [72]. Given that cognitive impairment related to alcohol use typically occurs after an extended period of extreme use [73], a longer period of follow-up may be necessary to determine the impact of AUDs on cognitive impairment in FES individuals. Also, assessments of global functioning [60] and quality-of-life measures do not appear to differ between FES individuals with and without AUDs [62]. Further research is needed to more closely examine the relationship between cognition, community functioning, physical health and co-occurring AUDs in FES individuals, especially with an emphasis on long-term outcomes. While it may be difficult to detect the impact of AUDs on the first few years of the clinical course of schizophrenia, AUDs during the first episode may promote chronicity later in life. Key characteristics of the studies reviewed in this section are presented in Table 3.

Maintenance stage of schizophrenia

The maintenance stage of schizophrenia can be characterized by a wide range of severity of the various groups of schizophrenia symptoms (i.e., positive, negative and disorganized), cognitive deficits and social dysfunction. As noted previously, more than 23% of individuals with schizophrenia have comorbid AUDs [20], and the majority of the literature examining the association between AUDs and schizophrenia has focused on patients in the maintenance phase.

■ Psychopathology

The most consistent finding within this phase of the illness is that AUDs are associated with increased positive symptoms (e.g., paranoia and auditory hallucinations), thought disorganization and depression [40,47,74–79]. Furthermore, Swendsen and colleagues monitored substance use and positive symptoms in real time and found that cannabis use preceded positive symptoms and anxiousness, while alcohol use

Table 3. Factors associated with alcohol-use disorders during the first episode of psychosis stage of schizophrenia.

Study (year)	Sample	Major findings	Ref.
Addington & Addington (2007)	n = 203 FES individuals (mean age: 25 years; SD: 8.38)	35% of FES individuals had a lifetime AUD. Comorbid AUDs were not associated with changes in positive or negative symptoms, depression, or quality of life	[62]
Barnett *et al.* (2007)	n = 123 FES individuals (median age: 25 years)	43.1% of FES individuals had a lifetime AUD	[58]
Compton *et al.* (2007)	n = 72 hospitalized FES individuals (mean age: 23.7 years; SD: 4.7)	36.1% of FES individuals used alcohol in the past 6 months; alcohol using and nonuse of alcohol individuals did not differ on length of hospital stay; alcohol use prior to hospitalization was associated with a greater likelihood of positive symptoms or aggression	[64]
Crebbin *et al.* (2008)	n = 251 FES individuals (mean age: 25.1 years; SD: 5.6)	35.1% of FES individuals had alcohol misuse[†]; alcohol misuse was not associated with increased days in hospital	[69]
Hambrecht & Hafner (1996)	n = 276 hospitalized FES individuals (or paranoid disorder; 12–59 years, mean age not reported)	23.7% of FES individuals had a lifetime AUD prior to hospitalization; comorbid AUD associated with more frequent auditory hallucinations, delusions, perceptual abnormalities and asocial behaviors	[59]
Kamali *et al.* (2006)	n = 100 FES individuals (mean age: 27.0 years; SD: 8.9)	8% of FES individuals had current AUD, which predicted medication noncompliance	[66]
Koskinen *et al.* (2009)	Meta-analysis across 60 studies	23.4% of SCZ had a lifetime AUD and 12.4% of SCZ had a current AUD. No difference in rates between FES and long-term patients	[20]
Kovasznay *et al.* (1997)	n = 96 FES individuals (mean age: 27 years for FES with SUDs; mean age: 28.5 years for FES with no SUD)	83.3% of FES individuals with a SUD had an AUD and 43.8% of FES individuals had a lifetime AUD. Comorbid SUDs in this sample were associated with greater psychiatric symptoms and lower functioning, but not medication noncompliance	[60]
Pencer & Addington (2003)	n = 266 FES individuals (mean age: 24.2 years; SD: 7.9)	12% of FES individuals had only an AUD, while 20% of FES individuals had an AUD with abuse or dependence on cannabis or hallucinogens. A comorbid AUD was not related to verbal fluency, visual–spatial ability, motor–speed, memory, executive function, visual attention or early information processing	[72]
Perkins *et al.* (2006)	n = 254 FES individuals (mean age: 23.9 years; SD: 4.8)	Lifetime or baseline alcohol use was not associated with medication noncompliance	[67]
Sorbara *et al.* (2003)	n = 58 FES individuals (mean age: 31.3 years; SD: 11.3)	A comorbid AUD in FES individuals was not related to hospitalization or involuntary admission during follow-up	[70]
Turkington *et al.* (2009)	n = 103 FES individuals; never used substances: n = 50 (mean age: 36.0 years; SD: 13.7); stopped substance use: n = 28 (mean age: 28.0 years; SD: 7.9); persistent substance use: n = 25 (mean age: 26.4 years; SD: 9.3)	33% of FES individuals had an AUD; FES individuals with persistent substance use had greater positive symptoms, relapse rates, depression and poorer functioning at 1-year follow-up. Specific effects of alcohol were not examined	[65]
Verdoux *et al.* (2000)	n = 65 FES individuals (mean age: 31.6 years; SD: 11.5)	30.8% of FES individuals had a lifetime AUD; medication noncompliance was associated with a comorbid AUD	[63]
Wade *et al.* (2006)	n = 103 FES individuals (mean age: 21.6 years; SD: 3.5)	30% of FES individuals had a lifetime AUD; a comorbid SUD was associated with increases in hospitalization and positive symptoms Specific effects of alcohol were not determined	[61]

[†]Clinical report of an alcohol problem or consuming above the government's recommended weekly limit.
AUD: Alcohol-use disorder; FES: First episode of psychosis; SCZ: Individuals with schizophrenia; SD: Standard deviation; SUD: Substance-use disorder.

tended to follow eruptions of positive symptoms and anxiousness [80]. These findings suggest that patients use alcohol as a means of coping with the stress of positive symptoms and anxiety. AUDs have also been associated with both greater [81], and lesser amounts [74,82] of negative symptoms.

■ Medication compliance & hospitalization

Surprisingly, the impact of AUDs on adherence to pharmacological treatment in individuals with chronic schizophrenia remains unclear. Some studies indicate that AUDs contribute to medication noncompliance in individuals with a more chronic form of the disorder [76], while

others present evidence to the contrary [83,84]. Also, some evidence suggests that other SUDs are associated with medication noncompliance [85,86], but do not provide evidence on the independent effects of alcohol. Medication noncompliance has been linked to both relapse [87] and rehospitalization [88] for individuals with schizophrenia. Thus, while the euphoric effects of alcohol may be used to achieve escape after experiencing positive symptoms and anxiety, this 'coping' strategy can lead to medication noncompliance. In turn, treatment noncompliance may then contribute to an increased risk for symptoms. Individuals with schizophrenia and comorbid AUDs are also at greater risk than noncomorbid patients to experience more drug side-effects, such as tardive dyskinesia [47,89], which may also contribute to treatment noncompliance.

Finally, cross-sectional research suggests that comorbid AUDs during the maintenance stage of schizophrenia are related to increased hospitalization [90–92] and longer hospital stays [91]. However, it is not clear whether AUDs contribute directly to hospitalization, or whether factors such as medication noncompliance, which are associated with rehospitalization [85,93], mediate this relationship.

■ Cognition & community functioning

Several studies suggest that individuals with schizophrenia and comorbid AUDs have exacerbated impairments in working memory [81,82,94,95], episodic memory [40,81,96,97], executive function [94–96], and verbal learning and memory [94]. However, the effect of AUDs on global cognition among individuals with chronic schizophrenia is somewhat unclear [82,96]. Given that cognitive function can undermine medication compliance [98,99], it is tempting to speculate that AUDs contribute to poor treatment compliance by contributing to cognitive impairment. Although some results failed to support this hypothesis [100], this study involved small study groups (n = 13 per group).

Deficits in vocation, independent living and social interaction are probably the most prominent characteristic of chronic schizophrenia [101]. Recovery-oriented interventions emphasize the need to improve the underlying causes of these disturbances with the goal of improving community functioning [102,103]. Recent studies examining the impact of AUDs on the community functioning of individuals with schizophrenia suggest that comorbid patients are at-risk for impaired social relationships [76,104]. Similarly, other forms of drug use among individuals with schizophrenia have also been associated with poor social functioning [105]. In addition to social functioning, Bowie and colleagues reported that individuals with schizophrenia and comorbid AUDs scored lower than noncomorbid patients on measures of everyday functional skills (e.g., finance management and communication) [81].

■ Physical health outcomes

AUDs have been identified as a risk factor for several chronic health conditions, including cancer, cardiovascular disease, hypertension and diabetes [48,49]. Individuals with schizophrenia at the maintenance stage of the disorder are at greater risk for these chronic health conditions [106–109], with nearly 50% of these patients self-reporting such problems [110]. A recent literature review supports an association between AUDs and chronic health conditions in schizophrenia [111]. This and other reviews compared the prevalence rates of several chronic health conditions in individuals with schizophrenia with and without AUDs [112] and found higher prevalence rates of asthma, chronic obstructive pulmonary disease, coronary artery disease, HIV, osteoarthritis, hypertension and hyperlipidemia [109,111], but not diabetes or hepatitis C [111] in the comorbid patients. Key characteristics of the studies reviewed in this section are presented in **Table 4**.

Clinical implications of comorbid AUDs across the stages of schizophrenia

Current evidence suggests that increased rates of AUDs occur across most, if not all, stages of schizophrenia. There is less certainty of this association in the premorbid and prodromal stages of schizophrenia, perhaps due to limitations in the duration of these early stages and variation in the operational definitions of AUDs [21,50]. Currently, treatments are being designed to prevent the transition of individuals from the premorbid and prodromal stages to later stages of schizophrenia [113–115]. These efforts would benefit from a more complete clinical and neurobiological understanding of the impact of AUDs on such transitions.

Given that FES individuals with AUDs are likely to have exacerbated psychopathology, it is important to examine the effectiveness of antipsychotic medication on this group. In one study, FES individuals with AUDs were less responsive to treatment with olanzapine than FES individuals without such comorbidities, while the

Table 4. Factors associated with alcohol-use disorders during the maintenance stage of schizophrenia.

Study (year)	Sample	Major findings	Ref.
Allen *et al.* (1999)	n = 54 SCZ_AUD (mean age: 43.1 years; SD: 13.1); n = 217 SCZ (mean age: 39.2 years; SD: 12.2); n = 231 individuals with an AUD (mean age: 41.7 years; SD: 13.2); n = 145 CON (mean age: 42.0 years; SD: 13.0)	A comorbid AUD in schizophrenia was associated with subtle additive deficits in cognition that became most prominent during the fifth age decade	[96]
Batki *et al.* (2008)	n = 80 SCZ_AUD (mean age: 42 years; SD: 9)	Negative symptoms were inversely correlated with alcohol use and alcohol cravings. A composite of positive and negative symptoms were correlated with alcohol craving	[74]
Batki *et al.* (2009)	n = 80 SCZ_AUD (mean age: 42 years; SD: 9)	Compared with SCZ [109], SCZ_AUD are at greater risk for hypertension, hyperlipidemia, osteoarthritis, asthma, COPD, coronary heart disease and HIV. Diabetes and Hepatitis C did not differ	[111]
Bowie *et al.* (2005)	n = 18 SCZ_AUD (mean age: 52.1 years; SD: 6.7); n = 17 SCZ (mean age: 54.9 years; SD: 10.7)	A comorbid AUD in schizophrenia was associated with greater negative and general symptoms; additive cognitive impairments in learning, delayed recall, digit span, working memory and an overall cognition score; deficits in community functioning skills such as planning, managing finances and an overall functioning score	[81]
Dixon *et al.* (1992)	n = 29 SCZ_AUD; n = 39 SCZ; n = 17 individuals with schizophrenia and comorbid SUDs (nonalcohol; mean age: 30.5 years; SD: 8.6)	A comorbid AUD was an independent risk factor for tardive dyskinesia	[89]
Drake *et al.* (1989)	n = 115 SCZ (mean age: 37.9 years; SD: 11.3).	Alcohol use was correlated with community dysfunction, threatening behavior, paranoia, disorganization, depression, chronic physical illness and medication noncompliance	[76]
Duke *et al.* (1994)	n = 53 SCZ_AUD (mean age: 43.4 years; SD: 14.9); n = 53 SCZ (mean age: 51.9 years; SD: 16.2)	Comorbid AUDs were associated with more severe hallucinations, anxiety, depression and tardive dyskinesia	[47]
Gerding *et al.* (1999)	n = 26 males with schizophrenia (mean age: 46 years; SD: 7)	Comorbid AUDs were associated with a greater risk for rehospitalization and longer hospital stays	[91]
Gupta *et al.* (1996)	n = 11 SCZ_AUD (with other SUDs; mean age: 37.1 years; SD: not reported); n = 11 SCZ (mean age: 40.8 years; SD: not reported)	Comorbid SUDs (alcohol was the most prevalent) were associated with a greater risk of rehospitalization	[92]
Jung *et al.* (2011)	n = 229 SCZ (mean age: 58.7 years; SD: 6.8); n = 125 CON (mean age: 58.6 years; SD: 6.4).	Schizophrenia inpatients had higher rates of osteoporosis compared with controls, while comorbid AUDs were associated with reduced bone density.	[109]
Hunt *et al.* (2002)	n = 38 SCZ (mean age: 41 years; SD: 2); n = 19 SCZ with a past history of SUDs (mean age: 33 years; SD: 2); n = 42 SCZ with a current SUD (mean age: 35 years; SD: 1)	23.8% had AUD only, 26.2% had an illicit SUD only, and 50% had polysubstance use (with alcohol). Patients with a comorbid SUD were at higher risk for rehospitalization	[86]
Koskinen *et al.* (2009)	Meta-analysis across 60 studies	23.4% of SCZ had a lifetime AUD and 12.4% of SCZ had a current AUD. No difference in rates between FES and long-term patients	[20]
Manning *et al.* (2009)	n = 30 SCZ_AUD (mean age: 36.6 years; SD: 10.2); n = 30 SCZ (mean age: 37.6 years; SD: 7.9); n = 30 CON (mean age: 35.9 years; SD: 7.5)	Additive cognitive impairments associated with a comorbid AUD in schizophrenia were found for delayed verbal memory, working memory, and executive functions such as set shifting and planning	[94]
Messias and Bienvenu (2003)	n = 80 SCZ_AUD (mean age: 33.8 years; SD: 11.5); n = 132 SCZ (mean age: 36.9 years; SD: 15.4)	A comorbid AUD was correlated with delusions of suspiciousness	[78]

AUD: Alcohol-use disorder; CON: Healthy control subjects; COPD: Chronic obstructive pulmonary disease; SCZ: Individuals with schizophrenia with no alcohol-use disorder; SCZ_AUD: Individuals with schizophrenia and a comorbid alcohol-use disorder or problematic alcohol use; SD: Standard deviation; SUD: Substance-use disorder.

Table 4. Factors associated with alcohol-use disorders during the maintenance stage of schizophrenia (cont.).

Study (year)	Sample	Major findings	Ref.
Mohamed *et al.* (2006)	n = 35 SCZ_AUD ages 45–54 years (mean age: 49.3 years; SD: 2.8); n = 17 SCZ_AUD ages 55+ (mean age: 64.9 years; SD: 7.7); n = 101 SCZ ages 45–54 years (mean age: 48.8 years; SD: 2.6); n = 119 SCZ ages 55+ (mean age: 64.4 years; SD: 6.9)	Older SCZ_AUD had greater impairments on episodic memory performance than older SCZ. Both groups had poorer cognition than the younger comorbid group	[97]

Nixon *et al.* (1996)	n = 13 SCZ_AUD (mean age: 34.3 years; SD: 6.8);
	n = 13 SCZ (mean age: 35.3v; SD: 10.8);
	n = 13 CON with an AUD (mean age: 38.0 years; SD: 5.1);
	n = 13 CON (mean age: 33.9 years; SD: 8.2)
		A comorbid AUD was not associated with additive cognitive impairments in attention and executive function	[100]

Olfson *et al.* (2000)	n = 172 medication-compliant individuals with schizophrenia (mean age: 37.6 years; SD: 9.6); n = 41 medication-noncompliant SCZ (mean age: 34.8 years; SD: 9.7)	The noncompliant group had a higher AUD rate than the compliant group (30.0 vs 20.9%, respectively), but it did not reach statistical significance	[83]
Osher *et al.* (1994)	n = 75 SCZ (mean age: 43.6 years; SD: 14.3)	25% (n = 19) of individuals with schizophrenia had a comorbid AUD. A comorbid AUD was correlated with hallucinations, thought disorder, bizarre behavior, and rehospitalization	[77]
Potvin *et al.* (2008)	Meta-analysis of 28 empirical studies	Working memory is negatively correlated with AUD among individuals with schizophrenia	[82]
Pristach and Smith (1990)	n = 23 SCZ_AUD (mean age: 35.5 years; SD: not reported); n = 19 SCZ (mean age: 35.8 years; SD: not reported)	Medication noncompliance did not differ between SCZ_AUD and SCZ	[84]
Pristach and Smith (1996)	n = 42 SCZ (mean age: 35.4 years; SD: 9.3)	54.8% (n = 23) of patients had a comorbid AUD. A comorbid AUD was associated with a greater frequency of hallucinations and paranoia	[79]
Pulver *et al.* (1989)	n = 63 SCZ_AUD; n = 159 SCZ (all mean age: 31.4 years; SD: not reported).	A comorbid AUD was associated with a greater likelihood of hallucinations and depression	[75]

Salyers and Mueser (2001)	n = 236 low/no alcohol SCZ (mean age: 30.1 years; SD: 7.9);
	n = 127 alcohol only SCZ (mean age: 29.4 years; SD: 7.1);
	n = 41 drug use SCZ (mean age: 26.3 years; SD: 5.1)
		'Low/no alcohol' schizophrenia patients had elevated social amotivation compared with the alcohol only patients. The 'alcohol only' schizophrenia patients had more problems with interpersonal relationships as compared with the low/no alcohol group	[104]

Schmidt *et al.* (2011)	n = 119 individuals with schizophrenia and a comorbid SUD (mean age: 41.2 years; SD: not reported); n = 107 individuals with schizophrenia and no substance-use comorbidity (mean age: 33.4 years; SD: not reported)	77% (n = 92) of the comorbid group had an AUD. Comorbid patients were more likely to be hospitalized and involuntarily hospitalized	[90]

Smith *et al.* (2011)	n = 16 SCZ_AUD (mean age: 38.6 years; SD: 14.7);
	n = 35 SCZ (mean age: 38.3 years; SD: 13.1);
	n = 56 CON (mean age: 38.2 years; SD: 12.1)
		The SCZ_AUD group was characterized by greater disorganized symptoms and an exacerbated episodic memory impairment when compared to the SCZ group	[40]

Swendsen *et al.* (2011)	n = 145 SCZ (mean age: 46.5 years; SD: 11.2)	Alcohol use followed anxious mood or psychotic symptoms. Alcohol use did not predict later psychosis, anxiousness, sad mood or event negativity	[80]

Thoma *et al.* (2006)	n = 9 SCZ_AUD (mean age: 46.8 years; SD: not reported);
	n = 9 SCZ (mean age: 36.8 years; SD: not reported);
	n = 8 individuals with an AUD (mean age: 47.8 years; SD: not reported);
	n = 9 CON (mean age: 37.8 years; SD: not reported)
		Additive cognitive impairments associated with a comorbid AUD in schizophrenia were found for working memory, attention, behavioral inhibition and sensory gating	[95]

AUD: Alcohol-use disorder; CON: Healthy control subjects; COPD: Chronic obstructive pulmonary disease; SCZ: Individuals with schizophrenia with no alcohol-use disorder; SCZ_AUD: Individuals with schizophrenia and a comorbid alcohol-use disorder or problematic alcohol use; SD: Standard deviation; SUD: Substance-use disorder.

treatment responses of these groups to haloperidol were similar [116].

Meanwhile, research has begun to compare the effectiveness of first- and second-generation antipsychotic medications for the treatment of individuals with schizophrenia and comorbid AUDs [117–119]. This evidence suggests that clozapine, as compared with risperidone [119] and other antipsychotic drugs [118,120], may reduce the use and misuse of alcohol. In summary, there is growing evidence that second-generation antipsychotic medications may reduce alcohol use and cravings more effectively than first-generation antipsychotic medications [121]. There is also evidence that naltrexone and disulfurate [122], and acrapromate [123] have been associated with the reduction of drinking behaviors in individuals with schizophrenia [124]. This therapeutic approach should be integrated with evidence-based psychosocial treatments [125,126] that reduce 'high-risk' behaviors that lead to substance use, and improve cognitive and social impairments [127,128].

Limitations

This article provides a novel approach to the impact of AUDs within the four stages of schizophrenia, as each stage has a distinct literature. Thus, academics and clinicians can use this article to identify areas for future research and intervention development relevant to each stage. There is limited generalizability of the reviewed findings as study samples were quite diverse across each stage. Although we conducted a thorough search of the literature, some relevant studies may have been overlooked based on limitations of our search criteria.

There are several limitations of the extant literature related to the intersection between schizophrenia and AUDs that need to be addressed in future work. Although each stage of schizophrenia is characterized by neuroanatomical abnormalities [4,11,15,19], the literature suggesting that AUDs exacerbate these abnormalities is quite limited. Hence, the clinical implications of these abnormalities are still unclear, and as such, more research is needed to examine whether they impact clinical outcomes. Most studies in this review were cross-sectional, which prevents causal inferences regarding the clinical implications of AUDs. For instance, it remains uncertain as to whether AUDs contribute to poor medication compliance, which in turn contributes to increased psychopathology and relapse risk. Benefits for clinical practice depend on the clarification of these causal relationships. As such studies are performed, it will be possible to develop a comprehensive conceptual model of the relationship between alcohol use and schizophrenia.

Although several studies have focused on the impact of AUDs in individuals with schizophrenia, it is common to include individuals with both alcohol- and cannabis-use disorders. Given that alcohol and cannabis have unique neurobiological effects that may interact differently with the underlying neurobiological substrates of schizophrenia [38,129,130], future studies of groups of subjects with a more limited range of SUDs are needed. Alternatively, the severity of use of confounding SUDs could be used as covariates during data analysis.

Finally, future studies examining the clinical implications of AUDs or other SUDs should consider variations in the selection and dosing of antipsychotic medications as well as the use of psychosocial treatments. Consideration of such variables will make study findings easier to interpret, since the literature suggests that some antipsychotic medications and psychosocial treatments may be more effective than others at reducing psychopathology, improving cognition and reducing drug craving.

Conclusion & future perspective

An elevated AUD prevalence rate is associated with each stage of schizophrenia, and this association may be related to neurobiological substrates, such as the brain's reward system, that have been linked to both schizophrenia and addiction. There are important clinical implications associated with comorbid AUDs in individuals with schizophrenia that demand clarification through additional research. At the early stages of schizophrenia, when the impact of alcohol use may be greatest, we know the least regarding its effects on psychopathology, cognition, community functioning, and most importantly, its effects on illness progression. Interventions designed to treat individuals at early stages of schizophrenia need to be developed with a consideration of the use of alcohol and other substances in mind. Furthermore, there is now substantial evidence that comorbid AUDs increase psychopathology, undermine medication compliance, increase the risk of relapse and rehospitalization, and add to cognitive impairment and chronic health conditions in individuals with more advanced stages

of schizophrenia. Over the next 5–10 years, longitudinal studies can be undertaken to clarify causative mechanisms, develop a conceptual model, and test novel interventions to improve the long-term outcome of schizophrenia.

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