Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis

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INTRODUCTION

Schizophrenia and addiction are both chronic disorders with serious complications, consequences, and costs for individuals and society. Both conditions are associated with poor adherence to treatment and poorer outcomes when the co-occurring disorder is present.

Some of the symptoms of schizophrenia overlap with symptoms of intoxication, chronic use, or withdrawal from alcohol or other drugs. Family history and the temporal relationship of symptoms can help to distinguish patients with a substance use disorder (SUD) alone from co-occurring schizophrenia and SUD.

The psychiatric diagnoses, substance abuse and substance dependence, in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) were replaced by one diagnosis, SUD, in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1]. Although the crosswalk between DSM-IV and DSM-5 disorders is imprecise, substance dependence is approximately comparable to SUD, moderate to severe subtype, while substance abuse is similar to the mild subtype.

The epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis of schizophrenia and SUD are described here. Treatment of co-occurring schizophrenia and SUD

are described separately. The epidemiology, pathogenesis, clinical manifestations, course, assessment, diagnosis and treatment of schizophrenia occurring alone and SUD occurring alone are also discussed separately.

- (See "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)
- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment".)
- (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment".)
- (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)
- (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)
- (See "Cocaine use disorder: Epidemiology, clinical features, and diagnosis".)

EPIDEMIOLOGY

Prevalence — Epidemiologic studies have generally shown that the prevalence of substance use disorder (SUD) is elevated in persons with schizophrenia compared with the general population. As examples, in a study of substance use among 9142 individuals with severe psychotic disorders, including 5586 subjects with schizophrenia or schizoaffective disorder, the odds of nicotine (smoking), alcohol, marijuana, and other drug use were higher (odds ratio 3.5 to 4.6) in patients with psychosis compared with 10,195 nonpsychiatric controls [2]. Rates of substance use varied among subgroups based on age, gender, and race or ethnicity. Having a psychotic disorder further increased the odds of substance use in each subgroup. The lifetime prevalence of the DSM-IV-TR disorders substance abuse and substance dependence among patients with schizophrenia has been estimated to range from 47 to 59 percent in the United States compared with 16 percent in the general population [3-5].

A 2018 systematic review and meta-analysis estimated prevalence rates of SUDs in patients diagnosed with schizophrenia or first episode psychosis in 123 reports between 1990 and 2017 [6]. The prevalence of any SUD was 41.7 percent, followed by any illicit drugs (27.5 percent), cannabis (26.2 percent), alcohol (24.3 percent), and stimulant use (7.3 percent).

Differences between schizophrenia patients and normal controls in substance use may be diminished when the effects of low socioeconomic status (common among schizophrenia patients) are taken into account [7-15]. High rates of co-occurrence have also been observed internationally (eg, in Australia, Switzerland, Italy, Germany, England, Turkey, and Norway) [16-19]. Many with these co-occurring disorders used two or more substances.

In the Epidemiologic Catchment Area study in the United States, 90 percent of patients with schizophrenia used nicotine [3]. Other substances used by 94 homeless subjects with schizophrenia spectrum disorder, ranked by prevalence, included [20]:

- Cannabis – 37 percent
- Alcohol – 34 percent
- Cocaine – 31 percent
- Amphetamines – 12 percent
- Opioids – 12 percent
- Hallucinogens – 4 percent
- Sedatives – 3 percent

Conversely, the prevalence of schizophrenia among SUD patients has also been studied. For example, in a sample of 22,615 people treated for illicit drug use disorders in Chile, the prevalence of schizophrenia and related disorders was 1.1 percent in those with cocaine use disorders, but 5.2 percent in those with cannabis use disorders [21].

Further information about use of specific substances by schizophrenia patients is described below:

- **Nicotine** – Nicotine was the most frequently used substance among United States persons with schizophrenia over their lifetime in the United States [3]. A meta-analysis of 42 studies on tobacco smoking among subjects with schizophrenia found an average prevalence of 61 percent [22]. In contrast to the general United States population, tobacco smoking has not declined among individuals with schizophrenia in recent decades [2]. Persons with schizophrenia additionally smoke more cigarettes with more numerous and deeper inhalations [23]. (See "Patterns of tobacco use", section on 'Cigarette use'.)

- **Alcohol** – An apparent decline in alcohol use disorders in schizophrenia patients in the 1990 and 2000s has been associated with the implementation of stricter criteria for the disorder in later editions of DSM through DSM-IV-TR [24]. (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)

- **Cannabis** – With the decline in alcohol use disorder beginning in the 1990s, cannabis overtook alcohol as the next most frequently abused substance after nicotine in this population. A meta-analysis of 35 studies involving 16 countries found a lifetime median of 27 percent for cannabis use in persons with schizophrenia [25]. However, the median lifetime prevalence for schizophrenia patients under 30 was 45 percent [25], and rates as high as 53 percent have been reported in first episode psychosis [26]. Further information about the co-occurrence of schizophrenia and cannabis use/use disorder is reviewed separately. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects", section on 'Adverse effects of cannabis use'.)

- **Stimulants** – A meta-analysis of 64 epidemiologic studies of patients with psychosis found a pooled prevalence rate of 8.9 percent for stimulant use disorder [7]. Among 9002 patients diagnosed with schizophrenia in a national patient registry study in Norway, 7.6 percent had a five-year prevalence of stimulant use disorder [19]. Estimates of stimulant use disorder varied widely, depending upon the country studied, the clinical setting, the prevalence of co-occurring cannabis use, the rate of affective psychosis, and the use of biological assays to confirm stimulant use. The type of stimulants used reflected the stimulants popular in the general population of the country studied (eg, cocaine in the United States and amphetamines in Australia), leading the authors to suggest that people with psychosis are influenced by the same socioeconomic drivers of drug use and choice as are other members of their communities.

  Approximately 15 percent of patients with schizophrenia were found to have co-occurring cocaine use in the 1990s' Epidemiologic Catchment Area study in the United States [3]. The more recent Clinical Antipsychotic Trials of Effectiveness study found that of 1432 patients with chronic schizophrenia, 36 percent reported using cocaine in the United States [27]. Those with a co-occurring cocaine use disorder had poorer overall functioning compared with patients with a co-occurring SUD with a substance other than cocaine [27].

- **Opioids** – Study of co-occurring schizophrenia and opioid abuse/misuse has been limited, with findings of generally low prevalence rates:

  - A retrospective study of medical records of 146 Finnish patients with schizophrenia found a prevalence of opioid use of 4.1 percent [28].

  - In a study of 219 opioid-dependent patients in Germany, only two (1 percent) met criteria for schizophrenia [29].

  - A study of 75 opioid-dependent patients in New York City found that eight (11 percent) reported symptoms consistent with schizophrenia [30].

- A study of 1437 patients with schizophrenia at substance abuse treatment centers across the United States found that 5.1 percent reported a problem with heroin, and 7.2 percent reported a problem with nonheroin opiates [31]. A lower proportion of patients with schizophrenia had problems with opiates compared with patients with depression or bipolar disorder or across substances.

- A study found that over 6 percent of a sample of 312 decedents of opioid overdose had received a schizophrenia related diagnosis over a 36-month period prior to their death [32].

- **Sedative/hypnotics** – There is increasing evidence available on the proportion of individuals with schizophrenia that have a sedative/hypnotic use disorder. As examples:

  - A 2015 survey of 9002 patients diagnosed with schizophrenia in a national patient registry in Norway found that 3.3 percent had a five-year prevalence of sedative use disorder [19].

  - Among the 1432 patients with schizophrenia in the Clinical Antipsychotic Trials of Intervention Effectiveness trial, 13.7 percent received anxiolytic drugs, and 11.2 percent received sedative/hypnotics.

  - In a 2017 survey of homeless subjects with schizophrenia spectrum disorders, 3 percent reported use of sedative tranquilizers in the year preceding examination [20].

  Sedative/hypnotics are widely prescribed in patients with schizophrenia as concomitant medications targeting agitation, anxiety and insomnia, even though they have been reported to have a high misuse potential, risk of drowsiness, blunted emotions, acute cognitive impairments, increased risk of dependence and withdrawal, and increased mortality in combination with antipsychotics [33,34].

- **Hallucinogens/psychedelics** – While there is limited evidence on the extent of abuse of psychedelic drugs among patients with or at risk of schizophrenia [20], popularization of the recreational and therapeutic use of these drugs, as well as approval of treatments with ketamine and its analogs for depression, are likely to lead to increasing concerns over misuse.

Risk factors — Studies suggest that patients with schizophrenia and one or more of the following risk factors are more likely to have a co-occurring SUD [35-37]:

- Younger
- Male

- Homeless
- Incarcerated
- Urban

Frequent cannabis use, especially at an early age, seems to be an important risk factor associated with development of schizophrenia [38,39]. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

PATHOGENESIS

Etiologic theories — Causes of the comorbidity between schizophrenia and substance use disorder (SUD) are not known. Etiological theories can be categorized into four groups: common factors, secondary SUD, secondary mental disorder, and bidirectional models [40,41]. These models vary in their extent of supporting evidence and are not mutually exclusive [42]. In any individual case, more than one mechanism may contribute to comorbidity.

- **Common factors** – This concept hypothesizes that the comorbidity results from risk factors common to both disorders. A shared genetic vulnerability has been proposed to underlie dysregulation in schizophrenia and substance abuse [41-44]. As examples:

  - The association between schizophrenia and cannabis use has been proposed to be due to a shared genetic predisposition [45,46].

  - A 2017 study investigating comorbid risk in SUD registries found strong associations between any SUD diagnosis and the polygenic risk score for schizophrenia [47].

  - Genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms in the human CHRNA5 gene, encoding the alpha-5 nAChR subunit, that increase the risks for both smoking and schizophrenia [48].

  - Impaired myelin development also has been studied as a possible precursor of both disorders [49].

  In addition to or as an alternative to genetic risk, early life environmental insults could cause developmental dysfunction in common neural circuitry pathways (eg, the mesocortical limbic dopamine system), underlying both disorders [41,42].

  The “primary addiction hypothesis” proposes both schizophrenia and SUD derive from a common pathophysiology [41]. Clinical and preclinical data suggest that the increased prevalence of SUD may result from the neuropathology underlying schizophrenia

disrupting brain reward circuitry [42,50]. Developmental irregularities in the hippocampus and prefrontal cortex could contribute both to the symptoms of schizophrenia and vulnerability to SUD [50]. The hippocampus and prefrontal cortex provide inhibitory control over dopamine-mediated behavior through interactions with the nucleus accumbens. In schizophrenia, abnormalities in the hippocampal-prefrontal regulation of dopamine activity in the nucleus accumbens could result in increased responsiveness to drug-stimulated dopamine release, facilitating the positive reinforcing effects of drug reward and reducing control over the inhibition of drug-seeking behavior [50,51].

Studies have also focused on common aberrations in cognitive executive function mapped to specific neural circuits as causative in patients with schizophrenia and SUD, which could be the result of genetic and/or environmental factors [52,53]. Evidence on neuropsychological performance, gray matter volume, and functional brain activation implicate transdiagnostic defects in neurocircuits underlying general cognitive control capacity [53-55]. Impairments in networks subserving adaptive and flexible cognition may render patients vulnerable to a broad spectrum of psychopathology. As an example, in a meta-analysis of studies involving cognitive control tasks across axis I disorders, a transdiagnostic pattern of aberrant brain activation was observed in regions corresponding to the multiple demand network, including the left prefrontal cortex (from premotor to mid-dorsolateral prefrontal cortex), the right insula extending to ventrolateral prefrontal cortex, right intraparietal sulcus, anterior mid-cingulate/presupplementary motor cortex, and anterior dorsal anterior cingulate cluster (as well as the insula) [54].

Any theory of causality for comorbidity must take into account and adjust for the confounding or contributing effect of common demographic and socioeconomic risk factors (the cumulative risk hypothesis) [41]. There is ample evidence that schizophrenia is diagnosed at a higher rate among disadvantaged, minority, and lower socioeconomic groups [8-11], which are also prone to higher rates of substance use and greater resistance to treatments for addiction [12-14]. It may be misleading to compare patients with schizophrenia with the general population without controlling for demographic and socioeconomic factors. People with schizophrenia have generally been found to use the substances that are readily available and affordable in their communities [7,15]. In a study comparing 97 smokers with serious mental illness (69 percent schizophrenia/schizoaffective disorder) and controls, the main reasons given for smoking were to relax and to cope with stress and boredom, which were associated with social and economic disadvantages [56].

- **Secondary mental disorder** – This model posits that SUD precipitates mental disorders in genetically predisposed individuals (the diathesis-stress or two-hit hypothesis) [41]. Retrospective studies report mixed results on the temporal relationship between the disorders [57], but more recent data appear to confirm the increased prevalence of SUD among youth at risk for schizophrenia [58-60].

  The strongest evidence for this model is from findings of a dose-related association between cannabis use and the subsequent onset of schizophrenia [41]. The significance of these findings remains controversial and a causative role has not been proven. The vast majority of cannabis users do not develop schizophrenia, and not everyone diagnosed with schizophrenia has been exposed to cannabis [61].

  Similar findings have been seen with other substances. A report of amphetamine-induced psychosis found that 25 percent of patients transitioned over several years into a more chronic psychosis diagnosed as schizophrenia in some patients [62]. A nationwide survey in Taiwan reported that a previous diagnosis of attention deficit hyperactivity disorder (ADHD) and treatment with methylphenidate were significant predictors of subsequent psychotic disorders [63]. The subgroup of patients with ADHD who were found to have the risk allele for schizophrenia (at rs1602565) in a genome-wide association analysis may be those more likely to develop psychosis in long-term follow-up studies with the use of psychostimulants [64].

A 2017 survey of patient registries in Denmark found that a diagnosis of any substance abuse increased the risk of developing schizophrenia, with cannabis and alcohol showing the strongest association when adjusted for poly-drug abuse [65]. However, diagnoses of hallucinogen abuse were associated with the highest risk for developing schizophrenia in unadjusted analyses and the highest proportion of schizophrenia diagnoses compared with other substances [65]. By contrast, a survey based on self-reports of people drawn from the annual United States National Survey on Drug Use and Health suggested that psychedelics were not associated with mental health problems or suicidality [66], but these findings were challenged and subsequently modified because of the confounding effect of poly-drug abuse in many users of psychedelics [67]. A 2018 study of chronic ketamine abusers found that 23 (31 percent) of 74 such patients developed persisting psychotic symptoms with greater symptom scores and impairments in spatial problem solving and verbal memory similar to schizophrenia patients [68]. Given the emergence of schizophrenia risk genes associated with glutamate synaptic signaling, the study raises the possibility that chronic ketamine abuse may unmask a latent vulnerability to schizophrenia.

A 2017 study using genetic variants associated with smoking initiation derived from genome-wide association databases summarized past evidence for smoking initiation as a predictor of schizophrenia but was unable to provide statistically significant evidence of a causal effect of smoking status on risk of schizophrenia [69]. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

- **Secondary substance use** – This model is also known as the "self-medication hypothesis," proposing that individuals with schizophrenia use substances to reduce their symptoms or to counteract secondary side effects of antipsychotic drug treatment [35,70]. As examples:

  - Patients with schizophrenia may use stimulants to reverse negative symptoms or depressed mood. Accumulating data support the idea that nicotine derived from smoking tobacco affects several neurotransmitter systems, including dopamine, and that certain neurocognitive deficits in schizophrenia associated with neurotransmitters (eg, reaction time, spatial working memory, sustained attention) are improved after nicotine administration [41,71].

  - Hydrocarbons derived from smoking tobacco (not related to nicotine intake per se) have been found to induce metabolism and lower plasma levels of antipsychotic drugs, thereby reducing side effects of these drugs [72].

  - Some patients with schizophrenia may abuse benzodiazepines to normalize social information processing and reduce anxiety associated with GABAergic abnormalities, as shown in a study comparing functional magnetic resonance imaging responses with lorazepam challenge between schizophrenia patients and controls [73].

  Most studies, however, do not support this hypothesis. Substances used by individuals vary and appear to be motivated by several factors in addition to the individual's symptoms. Observations that substance abuse precedes the onset of psychosis or neuroleptic treatment in 14 to 69 percent of schizophrenia cases further argues against the hypothesis [50].

- **Bidirectional** – This model suggests that the presence of either a mental disorder or SUD can contribute to the development of the other in a mutually reinforcing manner over time. This model is largely theoretical and lacks supporting evidence from research.

Neurobiology — The dopaminergic and glutamatergic systems are involved in the etiology of schizophrenia. A deficiency is postulated in the dopamine-mediated mesocorticolimbic brain reward circuits in people with schizophrenia [42]. Substances of abuse are believed to ameliorate this deficit. Drugs such as nicotine, alcohol, and cocaine may reinforce brain reward

pathways by increasing levels of dopamine in the nucleus accumbens of the limbic system. A specific example is cocaine, which blocks the dopamine transporter from reuptake of dopamine, thereby increasing the amount of dopamine in the synapse available to bind to and activate postsynaptic dopamine receptors [50]. Another example is nicotine, which is obtained by a high proportion of individuals with schizophrenia from smoking tobacco, and which affects the dopamine reward pathway by binding to nicotinic acetylcholine receptors in the midbrain [74]. These neurons project from the ventral tegmental area to the nucleus accumbens where dopamine release leads to experiences of reward, promoting impulsive, addictive behavior [50]. (See 'Epidemiology' above.)

Deficiencies in dopaminergic neurotransmission in the mesolimbic regions and anterior striatum may result in cravings, leading schizophrenia patients to be vulnerable to addiction. SUD may modify signal detection, improving negative effects of schizophrenia overall, even in the absence of antipsychotic medications [50].

Reduced dopamine neurotransmission to the prefrontal cortex may contribute to the negative symptoms of schizophrenia. In addition, dopamine deficits in the prefrontal cortex related to repeated exposure to drugs may impair this region's ability to modulate dopamine release in the nucleus accumbens accounting for decreased sensitivity to rewards in chronically addicted patients and their attempts to compensate for this deficit through compulsive drug use [51,75].

Several hypotheses and associated research address specific substances:

- **Nicotine** – Among the cognitive deficits in schizophrenia is visual-spatial memory. Hypofunction of cortical dopamine in the hippocampus of schizophrenia results in impaired performance in visual-spatial working memory. Nicotine obtained by smoking tobacco acts on the prefrontal cortex via activation by nicotine of dopamine release, leading to transient improvements in tasks and attention [76].

  Data from animal models are consistent with the self-medication hypothesis (ie, that schizophrenia patients smoke tobacco in part for the beneficial effects of nicotine on cognition). These studies found that agonist activity of nicotinic agents at the alpha-7 acetylcholine receptor in the hippocampus and anterior cingulate corrects the visual-spatial memory impairment, sensorimotor gating abnormalities, social abnormalities, and changes in striatal dopamine release that have been demonstrated in genetic and transgenic rodent models of schizophrenia [5,41,71].

  A 2016 systematic literature review of evidence from both animal and human studies reinforced evidence that nicotine obtained from smoking may be used to normalize (self-medication hypothesis) genetically-determined deficits in sensory gating and cognitive

processing due to dysregulation of alpha-7 and alpha-4 beta-2 subunit containing nicotine receptors [77]. However, alternative evidence was also cited supporting the concept that nicotinic receptor dysfunction impairs dopamine-dependent reward circuits which accounts for both negative and depressive symptoms in schizophrenia and predisposes to heavy smoking (common or shared vulnerability hypothesis) [77]. This may explain evidence of early, premorbid smoking behavior, which itself may contribute to the expression and early onset of schizophrenia.

GWAS identified single-nucleotide polymorphisms in the human CHRNA5 gene, encoding the alpha-5 nAChR subunit, that increase the risks for both smoking and schizophrenia [48]. In a study of mice with altered alpha-5 nAChR gene function that resulted in altered cognitive activity resembling hypofrontality deficits observed in schizophrenia and addiction, chronic nicotine administration reversed neurocognitive behavioral deficits in social interaction and sensorimotor gating tasks [48], providing some support for self-medication by cigarette consumption.

Further deficits in brain reward circuits accounting for risk of smoking were identified by functional magnetic resonance imagining in a study showing increased activation of the bilateral ventro-medial prefrontal cortex, a core region of the brain reward system, triggered by appetitive cigarette cues in 18 smokers with schizophrenia compared with 24 control smokers [78].

- **Cannabis** – Cannabinoids have been shown in animal models to modulate release of neurotransmitters implicated in psychosis, including dopamine and gamma-aminobutyric acid by activating cannabinoid-1 receptors (CB1) [79]. Preclinical evidence suggests that CB1-mediated increases in mesolimbic dopaminergic activity may explain the positive psychotic symptoms induced by tetrahydrocannabinol. Either too much or too little dopaminergic activity in the prefrontal cortex is associated with prefrontal cortex-related cognitive functions, leading to a bell-shaped relationship between dopamine levels and working memory efficiency [79]. Systemic administration of cannabinoids in the rat has been reported to increase prefrontal cortical dopamine release or turnover [80] and could account for the ability of cannabinoids to produce acute deficits in prefrontal cortex-related cognitive functions, such as working memory and attention [79]. Cannabinoid and dopamine receptor interactions in the prefrontal cortex, ventral tegmental area, and amygdala are thought to be related to the emotional associative learning difficulties in both SUD and schizophrenia [81]. Cannabinoids could also induce psychosis and cognitive impairment through actions on gamma-aminobutyric acid-ergic systems and

glutamatergic systems. Cannabidiol, another compound found in cannabis, can offset many of these effects [82].

The endocannabinoid system is critical to a number of neurodevelopmental processes that include axon elongation, neurogenesis, neural maturation, neural specification, glia formation, and neuronal migration [61]. These processes may be relevant to the neurodevelopmental hypothesis of schizophrenia. Perturbations of the endocannabinoid system in the rapidly changing brain, as is the case in adolescence, may have far reaching consequences [82]. Hippocampal hypertrophy has been associated with adolescent cannabis use [83]. Increased grey matter density in other limbic subcortical structures has been reported and may reflect cannabis-induced changes in arborization [84]. Reduced white matter integrity has been identified in adolescent cannabis users and appears to correlate with impaired neurocognitive functioning [85].

Although effects on neurotransmitter systems may account for some of the ability of cannabinoids to cause positive, negative, and cognitive symptoms, the mechanisms underlying the association between chronic cannabis use and psychotic disorders like schizophrenia remain poorly understood. It has been suggested that genetic factors may confer vulnerability to psychosis following exposure to cannabis. Preliminary evidence from candidate gene studies has identified a number of specific gene variants that may interact with cannabis to increase the risk of developing a psychotic disorder [86]. Studies have implicated polymorphisms in catechol-O-methyltransferase, other dopaminergic genes (eg, AKT1, dopamine receptor D2), *CNR1* (the gene encoding for CB1), brain-derived neurotrophic factor, and various others [86-92]. However, these gene association studies have failed to show consistent associations with cannabis use and psychosis [90,92].

Genome-wide association studies (GWAS) may better ascertain whether chronic cannabis use is causally associated with psychotic disorders such as schizophrenia [93]. A bidirectional two-sample Mendelian randomization was used to investigate a causal relationship between any history of lifetime cannabis use and schizophrenia using a schizophrenia GWAS (n = 36,989) [94] and GWAS of any lifetime cannabis use (n = 32,330) [95]. Single nucleotide polymorphisms associated with cannabis use and schizophrenia were combined. Some evidence was found to support the hypothesis that any lifetime cannabis use might increase the risk of developing schizophrenia, but the effect appeared small.

In contrast, strong evidence was found that schizophrenia risk increases the risk of cannabis use. A bidirectional two-sample Mendelian randomization was used to examine a causal relationship from cannabis use to schizophrenia and vice versa [96]. Weak, nonsignificant evidence was found for a casual influence of any lifetime cannabis use on schizophrenia risk

and much stronger evidence for a causal positive influence of schizophrenia risk on any lifetime cannabis use [97]. Mendelian randomization was used in a study finding strong evidence for the hypothesis that cannabis use is causally related to risk for schizophrenia (causality in the other direction was not tested) [98]. Using genetic data and applying population-based estimates, cannabis use was associated with an increased risk of schizophrenia of 37 percent.

Any conclusions derived from these three studies are limited by the lack of distinction in each cannabis GWAS between having tried cannabis once and having used it every day for many years [97,99]. The association between any lifetime cannabis use and psychosis is much weaker than that for heavy cannabis use [100]. Cannabis use was studied in 901 patients with first-episode psychosis in 11 sites across Europe and Brazil and 1237 population controls from the same sites [101]. Daily cannabis use was associated with increased odds of psychotic disorder compared with never users (adjusted odds ratio 3.2, 95% CI 2.2-4.1), increasing to nearly five times increased odds for daily use of high-potency types of cannabis (adjusted odds ratio 4.8, 95% CI 2.5-6.3).

The authors emphasize that their findings in no way imply that the cause of psychotic disorder is simple and attributable to a single factor such as cannabis use [99]. Cannabis is neither necessary nor sufficient to cause psychosis. More likely, it represents a component cause that interacts with other factors to cause psychosis [61]. The link between cannabis and psychosis may be moderated by age of onset of cannabis use, daily use of high potency cannabis, childhood abuse, and genetic vulnerability [61,87,97,99,102,103].

A study sought to further clarify gene-environment interactions in schizophrenia, analyzing the main and joint associations of polygenetic risk scores for schizophrenia and environmental exposures that have been associated with schizophrenia spectrum disorders in 1699 patients with a diagnosis of schizophrenia and 1542 unrelated controls [104]. Cannabis use was defined as once or more per week during the lifetime period of heaviest use. A polygenetic risk score for schizophrenia was constructed using schizophrenia summary statistics from the GWAS of schizophrenia [94]. Evidence was found for positive additive interactions of molecular genetic risk state for schizophrenia with the presence of lifetime regular cannabis use and exposure to early life adversities including sexual abuse, emotional abuse, emotional neglect, and bullying. No evidence was found for significant additive interaction effects with physical abuse, physical neglect, hearing impairment, or winter birth. The authors proposed that their study was the first to report that the sensitivity of adverse life events during childhood and exposure to cannabis is moderated by the genetic risk state for schizophrenia. Research in this area has grown particularly important with increasing access to cannabis for medicinal and recreational use.

- **Opioids** – Since N-methyl-D-aspartate (NMDA) receptors play important roles in the pathophysiology of substance misuse, rare variants in the NMDA-related genes have been hypothesized to exert effects on the risk for substance misuse. Regions of genes involved in the NMDA system were sequenced in subjects with co-occurring DSM-IV alcohol dependence, cocaine dependence, and opioid dependence, and healthy controls [105]. Eleven rare variants were successfully genotyped, and an association of these 11 rare variants with opioid dependence in African Americans was identified. Results from the gene-based association tests showed that the association signal derived primarily from DISC1 and GRIN2B. Furthermore, in their GWAS for opioid dependence [106], DISC1 was identified as a potential common variant associated with opioid dependence in both African Americans and European Americans. The authors note that DISC1 was originally identified as a schizophrenia risk gene [107], although it has now been linked to a variety of psychiatric and neuropsychiatric disorders. They speculate that their findings regarding DISC1 could represent a biological convergence of schizophrenia and opioid dependence risk.

The DISC1 gene polymorphism rs2738888 was genotyped in a sample of 392 Polish individuals diagnosed with alcohol and/or opioid dependence and a group of 257 controls [108]. An analysis of the data found an association between opioid dependence and DISC1 polymorphism rs2738888 and suggested a strongly protective effect of the polymorphism against opioid dependence.

There may be abnormalities in the cortical opioid system in schizophrenia [31]. Analysis of postmortem tissue found increased expression of mRNA for the mu-opioid receptor in the prefrontal region of patients with schizophrenia compared with controls [109]. Schizophrenia patients have decreased pain sensitivity compared with controls [110], although it is unclear if this relates to abnormalities in the endogenous opioid system [111]. There may be differences in the neurobiological pathways underlying opiate reward compared with other drugs of abuse [31]. Fourteen heroin addicts on methadone underwent two positron emission tomography scans of the dopamine system using carbon-11 raclopride following an injection of either a placebo or an opioid agonist [112]. No increase in striatal dopamine levels was observed despite marked opioid effects. In contrast to other drugs considered above, these findings suggest that increased dopaminergic activity in the ventral striatum may not be related to the opioid "high" observed in humans. In the case of opioids, sites other than the dopamine system may mediate their addictive actions. It has been suggested [113] that other output regions of the basal ganglia dopamine projections, such as the globus pallidus, have high opioid receptor densities and could represent the downstream targets for mu-opioid agonists.

- **Hallucinogens/psychedelics** – This class of drugs is unique in producing reactions that closely simulate symptomatic, informational and cognitive processing, and electrophysiological features of schizophrenia, such that they have been used as pharmacological models of mechanisms underlying schizophrenia. Thus, in individuals at risk for schizophrenia, use of these drugs may synergize with genetic or underlying neurotransmitter abnormalities to precipitate overt expression of psychotic symptoms [114], or at least, present a challenging diagnostic dilemma between toxic iatrogenic versus endogenous idiopathic causality. Pharmacologic models fall into three classes of psychedelic drugs based on neurotransmitter properties; dopaminergic stimulants (amphetamines, cocaine); glutamate NMDA receptor antagonists (eg, ketamine, phencyclidine, and dizocilpine) [68,114,115]; and serotonergic 5-HT2A/C agonists (eg, psilocybin, N,N-diethyllysergamide, and N,N-dimethyltryptamine) [116,117].

CLINICAL MANIFESTATIONS

Substance use can initially cause euphoria or confusion, which may simulate or obscure symptoms of schizophrenia and social frustrations, thereby promoting continued use. With chronic use, however, substances may aggravate symptoms of schizophrenia and could result in treatment failure and more frequent acute psychotic episodes. Adverse effects of ongoing substance use on control of psychotic symptoms may reflect direct psychoactive effects of substances themselves, pharmacokinetic effects on antipsychotic plasma levels, or poor treatment adherence. (See 'Course' below.)

Schizophrenia patients with co-occurring substance use have higher rates of positive symptoms compared with patients with schizophrenia but no substance use and higher rates of violence. A meta-analysis of 22 studies comparing patients with psychotic disorders who did or did not have concurrent substance use found that substance users had a greater severity of positive symptoms compared with nonusers, but did not differ in negative symptoms, depressive symptoms, suicidal ideation, or the number of hospitalizations [118]. It is possible that these findings were confounded by sociodemographic characteristics of the samples (younger age and more males among substance users). This as well as a subsequent meta-analysis also found that concurrent substance use was a risk factor for violence among patients with psychotic disorders [118,119]. In an analysis of data from the Clinical Antipsychotic Trials of Interventions Effectiveness study, schizophrenia patients with comorbid substance use showed more general psychopathology, including greater depressive symptoms and lower quality of life, compared with nonusers [37].

Studies in patients with schizophrenia and substance use disorder (SUD) have identified multiple types of cognitive deficits. In a 2017 study, 50 patients with dual diagnoses showed low executive function performance in set-shifting, planning, and problem solving tasks [120]. Those with suicide attempts demonstrated even worse problems with solving skills and decision making compared with nonattempters. Defects in executive function were related to the premorbid intelligence quotient, the duration, severity, months of abstinence and relapses of SUD, global functioning, and negative symptoms. A relationship between current suicide risk and first-degree relatives with SUD, patient insight and positive symptoms was also found. In a separate systematic review, patients with schizophrenia and SUD showed less inhibitory control but variable shifting abilities on neuropsychological testing compared with patients with schizophrenia alone [55].

Abnormalities in function of the salience network, which is dependent on brain structures involved in a cortico-striato-thalamo-cortical loop and implicated in disorders of cognitive control and self-regulation, have also received increasing attention as a common link underlying schizophrenia and SUD [53].

More heterogeneous findings were reported in a 2017 systematic literature review of structural and functional neuroimaging that compared patients with schizophrenia and SUD, schizophrenia alone, SUD alone and healthy controls [121]. Both schizophrenia patients with or without SUD were more impaired than healthy controls or SUD patients in most studies. Schizophrenia patients with SUD initially showed better neurocognitive functioning during the first years of illness compared with those without SUD, but after five years, the former group exhibited significant, progressive increases in brain alterations and impairment.

Individual classes of substances are associated with differing presentations in schizophrenia patients with substance use:

- **Nicotine** – Patients with schizophrenia who are heavy tobacco smokers have been found to experience increased hallucinations and delusions (positive symptoms) but decreased negative symptoms in comparison with nonsmokers and light smokers [23].
- **Alcohol** – Patients with schizophrenia and a co-occurring DSM-IV-TR alcohol abuse/dependence have been shown to have:
  - A greater severity of depressive symptoms and hallucinations than schizophrenic patients without alcohol abuse/dependence [122].
  - Impairment of cognition beyond that associated with the schizophrenia – Impairments include deficits in problem solving, and difficulty retaining and utilizing treatment

recommendations [123].

- **Cannabis** – Multiple studies have found that patients who develop schizophrenia following cannabis exposure exhibit more severe positive symptoms [124-126] and fewer negative symptoms [38,127-129] compared with patients without cannabis use. However, not all reports have replicated these findings [130] and all studies are limited by their cross-sectional design [61]. Contrary to expectations, a substantial number of studies have reported that cannabis using schizophrenia patients showed better cognitive performance than nonusers [5,131]. One explanation proposed to explain this is that better cognitive performance may be driven by a subgroup of cognitively less impaired individuals who only developed psychosis after a relatively early initiation into cannabis use [132].

- **Stimulants** – Co-occurring cocaine use disorder and schizophrenia are associated with greater depressive symptoms and memory impairment compared with patients with schizophrenia without a cocaine use disorder [133]. Stimulants can exacerbate psychosis in patients with schizophrenia; for example, in a retrospective survey of 347 patients in Australia with schizophrenia, a significantly higher past-year prevalence of hallucinations, persecutory delusions, racing thoughts, dysphoria, and anhedonia was found among the 32 percent of schizophrenia patients who had used amphetamines in the past year [134].

- **Hallucinogens/psychedelics** – In a study of 80 schizophrenia patients with prior N,N-diethyllysergamide (LSD) use, 37 (46 percent) developed a persisting perceptual disorder [135]. Patients with persisting perceptual symptoms also were more likely to have experienced "bad trips," but showed fewer negative symptoms and general psychopathology. In early open, anecdotal studies using LSD in treatment of schizophrenia, either no benefit or significant worsening of symptoms were reported [115,136,137].

Several studies have sought to identify clinical features distinguishing between primary psychoses and stimulant-induced psychoses:

- In a study of cocaine use and psychosis, patients with cocaine-induced psychosis were more likely to have previous incarceration and visual hallucinations, whereas psychoses judged to be independent of cocaine use were associated with grandiose delusions and disorganized speech [138]. A resulting model predicted the diagnosis of lifetime cocaine-induced psychosis with a sensitivity of 80.3 percent and a specificity of 78.2 percent.

- A literature review found similarities in symptoms and cognitive function between patients with amphetamine-induced psychosis versus primary psychosis except for vivid visual hallucinations in the former group [139].

- In an attempt to distinguish methamphetamine-associated psychosis from schizophrenia based on imaging of brain dysfunction, 21 patients with amphetamine psychosis were compared with 14 schizophrenia patients and 21 controls using near-infrared spectroscopy during an inhibitory task [140]. Both patient groups showed common findings of reduced activation in the bilateral ventrolateral prefrontal cortex but only the methamphetamine group showed reduced activation in the frontopolar prefrontal cortex consistent with impairment in task performance.

- A 2018 study of 109 patients used electroencephalograms to measure the ratio of delta to alpha activity as an effective neurophysiological biomarker of psychosis and to determine differences between schizophrenia, bipolar disorder, methamphetamine-induced psychosis, and controls. Findings included higher delta/alpha frequency activity in patients with schizophrenia and methamphetamine psychosis than controls, with the investigators concluding that the pattern of response across brain regions and task conditions support the involvement of thalamo-cortical mechanisms in psychotic disorders and may provide a useful neurophysiological biomarker to delineate the psychotic disorders [141].

COURSE

Patients with moderate to severe substance use disorder (SUD) have an earlier age of onset of schizophrenia than patients without SUD. The SUD can either precede or develop subsequent to schizophrenia. In a study of 262 patients with first-episode schizophrenia in Europe and North America, 37 percent of patients had a premorbid history of a DSM-IV SUD [124]. A study of 404 patients with first episode schizophrenia found that 51.7 percent already met criteria for lifetime alcohol or drug use disorders [58].

The effects of schizophrenia and SUD are bidirectional. SUD worsens the course of schizophrenia and schizophrenia worsens the course of addictions. Though patients with schizophrenia may use less drugs and alcohol than SUD patients without schizophrenia, they may suffer more adverse consequences from the effect of substance use on the symptoms, course, and treatment of their mental disorder [40].

Clinical and psychosocial outcomes — The course of patients with schizophrenia and a co-occurring SUD, compared with patients with schizophrenia alone, has been found to have higher rates of treatment nonadherence and adverse life events including [18,142-149]:

- Medical comorbidity
- Hospitalization and longer hospital stays

- Homelessness
- Unemployment
- Violence
- Arrests/incarceration
- Earlier and higher mortality rate
- Suicide

As examples:

- A record-linkage study in Denmark showed that use of amphetamines robustly elevated risk of readmission for schizophrenia among 634 patients with a history of schizophrenia and a current substance use, but a less robust association with use of cannabis, and no association with cocaine, opioids, alcohol, benzodiazepines, and 3,4-methylenedioxy-methamphetamine [149].

- A seven-year prospective study of 150 patients with schizophrenia and SUD followed the course of patients with access to integrated treatment services in urban community mental health centers [150]. Patients improved significantly in absence of psychiatric symptoms, remission of SUDs, independent housing, competitive employment, and life satisfaction but not in social contacts. Despite improvements in these measures, overall recovery was mixed and variable; nearly half of the participants did not attain independent living and sizeable minorities continued to be hospitalized, incarcerated, or unemployed.

- In a study of smoking cessation, quitting smoking was not detrimental and was not associated with heightened binge drinking or symptoms of depression and anxiety among smokers with severe mental illness, including schizophrenia spectrum disorders [151].

A co-occurring SUD has been associated with a poorer outcome of first-episode schizophrenia resulting in [124,152,153]:

- Greater symptom severity
- More negative symptoms
- Longer period of untreated illness
- Poorer response to antipsychotic medications
- Lower rates of symptomatic and functional remissions

A longitudinal 10-year follow-up study of 266 first-episode patients showed that patients who were able to stop using substances within the first two years after diagnosis had outcomes similar to those who had never used with fewer symptoms than episodic or persistent users, supporting the importance of early intervention to address substance use [153]. However,

results from the RAISE-ETP study, a randomized, controlled study of usual care compared with a coordinated specialty care service that includes optional substance abuse content (NAVIGATE) in 404 first-episode patients, found that neither treatment nor time in treatment had an effect on days of self-reported substance use over the two-year follow-up [154].

Antipsychotic side effects — While some studies have suggested that rates and severity of extrapyramidal side effects (EPS) and tardive dyskinesia (TD) may be higher in schizophrenia patients with SUD (or substance use) compared with no SUD (nonusers), larger trials conducted in the United States and in Europe have not supported these findings:

- A clinical study of 106 consecutive, male patients with schizophrenia found that cocaine use was associated with severity of dyskinesia, parkinsonism, and akathisia [155].
- A clinical trial of 77 schizophrenia outpatients with SUD treated with antipsychotics found that alcohol and cocaine use was associated with more severe parkinsonian symptoms compared with nonusers [156]. Patients with substance use also had a higher severity of akathisia and lower severity of TD, though these differences did not reach statistical significance.
- Evidence suggesting that smoking might represent a risk for TD has been mixed, but a 2018 review of data on risk factors suggested a strong correlation between the amount of current cigarette consumption and TD severity, as well as a significant correlation between changes in current cigarette consumption and changes in TD severity [157].
- Among 212 patients with TD at baseline in the Clinical Antipsychotic Trials of Interventions Effectiveness trial of antipsychotics in 1432 patients with chronic schizophrenia, alcohol and stimulant use were both associated with the presence of TD at baseline, but data on outcomes during up to 18 months of antipsychotic treatment in the trial did not show differences in the emergence of new-onset EPS or TD between patients with and without substance use [158].
- In the European First Episode Schizophrenia Trial of antipsychotic treatment in 498 patients with first-episode schizophrenia, no differences were seen in rates of treatment-emergent EPS in first-episode patients with and without SUD [159].

  (See "Tardive dyskinesia: Prevention, treatment, and prognosis" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

Medical comorbidities — Patients with schizophrenia and a co-occurring SUD have been found to have higher rates of tuberculosis, HIV, hepatitis B, hepatitis C, and sexually transmitted diseases compared with patients with schizophrenia alone [160,161]. They have more smoking-related illnesses such as chronic obstructive pulmonary disease (COPD) and cardiovascular diseases. The rate of COPD in patients with schizophrenia and a co-occurring SUD has been found to be 22.6 percent compared with 7.6 percent in the general population [162]. Patients with schizophrenia have high rates of numerous cardiac risk factors (smoking, obesity, diabetes, hypertension, hyperlipidemia) compared with the general populations. SUD is associated with increased rates of these risk factors as well [163].

Greater rates of medical comorbidity, homelessness, and hospital readmission contribute to higher medical expenses, earlier mortality, and higher rates of suicide among patients with the co-occurring disorders, compared with schizophrenia alone. A 15-year follow-up study of the impact of SUD on schizophrenia patients found a mean age of death of 49.2 compared with mean age of 62.6 among patients with schizophrenia without SUD [164]. Suicide as the cause of death occurred more often in schizophrenia patients with SUD than without [164]. High rates of smoking have been implicated in high rates of medical comorbidity and premature deaths in people with schizophrenia [165]. (See "Health care of people experiencing homelessness in the United States".)

In a case-controlled study of the association between benzodiazepine use and pneumonia in 34,929 patients with schizophrenia in a national database in Taiwan, several benzodiazepines had a dose-dependent effect increasing the risk of pneumonia compared with controls [34].

SCREENING

Patients with schizophrenia should be routinely screened for the presence of a co-occurring substance use disorder (SUD). A national panel suggested routine use of validated, age-appropriate screening tools, based on findings of low rates of detection and treatment of comorbid serious mental illness and DSM-IV SUDs [166]. While not optimal, the CAGE-AID has demonstrated validity in screening individuals with mental disorders for dual diagnosis (table 1) [167]. Individuals with positive screening results should have a full diagnostic assessment. Despite the alarming rates and potentially serious health implications of smoking among people with schizophrenia, psychiatrists appear to be screening for smoking and providing effective anti-smoking treatments at declining rates [168].

ASSESSMENT

Clinicians should have a high index of suspicion for a comorbid substance use disorder (SUD) when assessing patients with schizophrenia, given high rates of co-occurring disorders in this population. A nonjudgmental approach to raising questions about patient substance use is essential. Patients may be reluctant to disclose information about these conditions due to stigma, shame, or other reasons. (See 'Prevalence' above.)

A thorough evaluation of a patient with schizophrenia for an SUD includes a comprehensive history from the patient, caregivers, and other collateral sources, a physical exam, and urine or blood toxicology. (See "Substance use disorders: Clinical assessment".)

Assessment with the Time Line Follow Back Scale can determine the frequency of SUD in temporal relationship to onset of psychotic exacerbations [169].

The clinician needs to ask explicitly about suicidal ideation. If there was a history of past suicide attempts, it is useful to ascertain whether the patient was intoxicated, withdrawing, or amid chronic use at those times. (See "Suicidal ideation and behavior in adults".)

The Addiction Severity Index (ASI) is helpful in determining lifetime, as well as current, alcohol and drug use [170]. Assessment with the ASI provides quantitative assessments of substance-related problems and days with substance use that can be monitored over time [171]. The ASI may be challenging to administer to a patient experiencing psychotic symptoms.

DIAGNOSIS

Substance use disorder in DSM-5 — A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12-month period [1]:

- The substance is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control use of the substance
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- Craving or a strong desire or urge to use the substance
- Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home

- Continued use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by its effects
- Important social, occupational, or recreational activities are given up or reduced because of use
- Recurrent use in situations in which it is physically hazardous
- Use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Tolerance
- Withdrawal

The current severity of a DSM-5 substance use disorder (SUD) can be specified as a subtype based on the number of symptoms present:

- Mild: Two to three criteria met
- Moderate: Four to five criteria met
- Severe: Six or more criteria met

The diagnoses, substance abuse and substance dependence, in DSM-IV-TR, were replaced by SUD in DSM-5. Most clinical trials of treatments for SUD with comorbid schizophrenia were conducted in samples limited to patients with substance dependence. Applying these findings to patients diagnosed under DSM-5 is imprecise, but the most closely comparable patients are those with SUD, moderate to severe subtype.

Schizophrenia in DSM-5 — DSM-5 diagnostic criteria for schizophrenia are described below [1]:

- A. Two or more of the characteristic symptoms below are present for a significant portion of time during a one-month period (or less if successfully treated):
  - 1. Delusions
  - 2. Hallucinations
  - 3. Disorganized speech (eg, frequent derailment or incoherence)
  - 4. Grossly disorganized or catatonic behavior
  - 5. Negative symptoms (ie, affective flattening, alogia, or avolition)
- B. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly

below the level achieved prior to the onset. When the onset is in childhood or adolescence: failure to achieve expected level of interpersonal, academic, or occupational achievement.

- C. Continuous signs of the disturbance persist for at least six months. The six-month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A that present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

- D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

- E. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse or medication) or a general medical condition.

- F. If the patient has a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Diagnostic specifiers for schizophrenia in DSM-5 are described separately. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Specifiers for schizophrenia in DSM-5-TR'.)

Differential diagnosis — In a patient with acute or chronic substance abuse newly presenting with psychosis, a careful diagnostic assessment is needed to distinguish first-episode psychosis from psychosis secondary to an SUD. Both schizophrenia and DSM-IV SUDs have been found to have a typical initial onset between late adolescence to early adulthood [50]. A family history of schizophrenia or an SUD, a detailed history that includes the temporal relationship of symptoms, collateral sources, and toxicology testing for abused substances can inform the diagnosis. Physical and neurological examination may reveal systemic or peripheral symptoms and signs of substance use (eg, track marks, formication [Magnan-Saury sign], tremors). Differentiating between these disorders can require continued observation and assessment over an extended period, between one and six months.

Several substances can cause psychosis during periods of intoxication, chronic use, or withdrawal [172]:

- Intoxication with stimulants, marijuana, or hallucinogens (see "Cocaine use disorder: Epidemiology, clinical features, and diagnosis", section on 'Acute intoxication' and "Intoxication from LSD and other common hallucinogens", section on 'Neuropsychiatric effects')
- Chronic use of stimulants or hallucinogens (see "Intoxication from LSD and other common hallucinogens", section on 'General clinical features of intoxication' and "Cocaine use disorder: Epidemiology, clinical features, and diagnosis")
- Withdrawal from alcohol and sedative hypnotics (see "Management of moderate and severe alcohol withdrawal syndromes", section on 'Alcoholic hallucinosis')

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Opioid use disorder and withdrawal" and "Society guideline links: Benzodiazepine use disorder and withdrawal" and "Society guideline links: Alcohol use disorders and withdrawal" and "Society guideline links: Stimulant use disorder and withdrawal" and "Society guideline links: Cannabis use disorder and withdrawal".)

SUMMARY AND RECOMMENDATIONS

- Individuals with schizophrenia have been found to be more than twice as likely to have a substance use disorder (SUD) compared with the general population, but these differences may diminish when controlled for common demographic and socioeconomic factors. Nicotine is the most commonly used substance, followed by cannabis, alcohol, and cocaine. (See 'Epidemiology' above.)
- Etiological theories on the development of co-occurring schizophrenia and SUD can be categorized into four groups (see 'Etiologic theories' above):
  - Common factors – Shared risk factors give rise to both disorders
  - Secondary mental disorder – SUD precipitates mental disorders in genetically predisposed individuals

- Secondary SUD – Individuals with schizophrenia use substances to reduce symptoms, antipsychotic side effects
- Bidirectional – Either disorder can contribute to the development of the other in a mutually reinforcing manner

- Substance use can initially cause euphoria or confusion, which may obscure symptoms of schizophrenia and offset social frustrations, thereby promoting continued use. With chronic use substances may aggravate symptoms of schizophrenia, impede treatment, and result in more frequent acute psychotic episodes. (See 'Clinical manifestations' above.)

- Compared with patients with schizophrenia alone, patients with schizophrenia and a co-occurring SUD have been found to have higher rates of treatment nonadherence and adverse life events, including (see 'Course' above):
  - Medical comorbidity
  - Hospitalization
  - Homelessness
  - Unemployment
  - Violence
  - Arrests/incarceration
  - Earlier mortality
  - Suicide

- Patients with schizophrenia should be routinely screened for the presence of a co-occurring SUD. While not optimal, the CAGE-AID has demonstrated validity in dual diagnosis populations (table 1). (See 'Screening' above.)

- A thorough evaluation of a patient with schizophrenia for SUD includes a comprehensive history from the patient, caregivers, and other collateral sources, a physical exam, and urine or blood toxicology. (See 'Assessment' above.)

- Co-occurring schizophrenia and SUD are diagnosed using the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. A careful diagnostic assessment is needed to distinguish a first-episode psychosis in schizophrenia from psychosis related to intoxication, chronic use, or withdrawal from an abused substance. (See 'Assessment' above and 'Substance use disorder in DSM-5' above and 'Schizophrenia in DSM-5' above.)

- In a patient with acute or chronic substance abuse newly presenting with psychosis, a careful diagnostic assessment is needed to distinguish first-episode psychosis from psychosis secondary to an SUD. A family history of schizophrenia or an SUD, a detailed history that includes the temporal relationship of symptoms, collateral sources, and toxicology testing for abused substances can inform the diagnosis. Physical and neurological examination may reveal systemic or peripheral symptoms and signs of substance use. (See 'Differential diagnosis' above.)

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