Caring for youth with co-occurring substance use and severe psychiatric disorders: diagnostic challenges and clinical implications

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Abstract:
Appropriate interventions for psychiatric conditions that commonly emerge during adolescence and early adulthood play a crucial role in modifying both acute risks as well as long-term outcomes. Substance use disorder is a common comorbidity during the early stages of mood and psychotic disorders that further heightens acute risks and is considered a negative prognostic factor. New presentations of mood and psychotic symptoms with co-occurring substance use are inherently challenging to formulate due to the uncertainty surrounding the relative impact of multiple intrinsic and extrinsic factors. Given such uncertainty, it is natural for clinicians to rely on heuristics to guide assessment and management. These heuristics however may bring about premature diagnostic closure by favouring the primacy of substance use, which in turn can result in a missed window of opportunity for a timely and appropriate intervention. We caution clinicians against over-attributing early symptoms of mood and psychotic disorders to substances use alone.

Résumé:
Les interventions appropriées pour les troubles psychiatriques qui apparaissent communément durant l'adolescence et le début de l'âge adulte jouent un rôle essentiel dans la modification tant des risques aigus que des résultats à long terme. Le trouble d'utilisation de substances est une comorbidité commune durant les premières phases des troubles de l'humeur et psychotiques qui hausse davantage les risques aigus et est considéré comme un facteur pronostic négatif. Les nouvelles présentations des symptômes de l'humeur et psychotiques avec un trouble concomitant d'utilisation de substances sont intrinsèquement difficiles à formuler en raison de l'incertitude entourant l'effet relatif de multiples facteurs intrinsèques et extrinsèques. Devant cette incertitude, il est naturel pour les cliniciens d’employer l’heuristique pour guider l’évaluation et la gestion. Ces heuristiques peuvent toutefois provoquer la clôture d’un diagnostic prématuré en favorisant la primauté de l’utilisation de substances, qui à son tour peut entraîner une fenêtre d'opportunité manquée pour une intervention ponctuelle et appropriée. Nous mettons en garde les cliniciens contre l’attribution excessive des symptômes précoces de l’humeur et des troubles psychotiques à la seule utilisation de substances.
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Clinical vignette
You are about to discharge a 17-year-old youth with no previous psychiatric history who was admitted to the inpatient psychiatric unit about 10 days ago with a 2-week history of persecutory delusions and disorganized behaviours. This occurred after a first time use of LSD and in the context of daily cannabis use with increasing tolerance and cravings over the last 4 months. The patient has been abstinent from recreational substance use throughout their admission but required frequent as-needed antipsychotic medications for severe anxiety related to persecutory delusions up until day 7 of admission. Though it is reassuring that their anxiety and delusions have now mostly remitted, you suspect that the patient still has some lingering persecutory beliefs regarding the hospital staff. In a family meeting, the patient’s parent asks “What caused this paranoia? Will this happen again? What should we do next?”

Introduction
The transition from adolescence to young adulthood is a critical developmental period characterized by challenges related to identity formation, autonomy, career establishment, and intimacy [1]. Although most adolescents manage to overcome these challenges and successfully navigate the transition to adulthood, for many others with genetic and environmental vulnerabilities, such transition can be further complicated by the emergence of psychopathology as well as substance use. In fact, a recently published large-scale epidemiological meta-analysis showed that over 62% of all mental illnesses emerge before age 25 with almost identical peak age at onset for mood disorders (20.5 years), psychotic disorders (20.5 years) and substance related disorders (19.5 years) [2].

The rates of substance use disorders (SUD) are significantly higher in individuals with mood and psychotic disorders when compared to the general population [3–5]. Estimates of concurrent SUD range from 20-30% in adolescents with depressive disorder [6], 16-48% in adolescents with bipolar spectrum disorders [7], and 24-74% in first episode psychosis [8]. Among adolescents receiving treatment for SUD, psychiatric comorbidity is estimated to range from 55-88%, with conduct disorder, attention-deficit/hyperactivity disorder (ADHD), depression, and anxiety disorders being the most common [6]. There are various ways in which co-occurring substance use can complicate mood and psychotic disorders:

• Stigma and discrimination (including self-stigma, stigma by society, and stigma from healthcare professionals): may impact help-seeking behaviour as well as the quality of care that patients with concurrent disorders may receive.
• Substance use can exacerbate the mental illness by limiting response to treatment and increasing risk of relapse [9]. Of particular concern, concurrent substance use is associated with significantly elevated risk of suicide in mood [10, 11] and psychotic disorders [11, 12].
• Recreational substances may interact with psychotropic medications.
• Substance use may interfere with an individual’s ability to follow up with treatment recommendations, e.g., attending therapy sessions, medication adherence, financing out of pocket expenses.
• Diagnostic challenges: substance use can imitate or mask symptoms of mental illness.

In this article, we focus on the last point with a particular emphasis on early presentations of mood and psychotic disorders. We start by discussing the clinical dilemma faced by clinicians when encountering youth with co-occurring substance use and recent-onset mood or psychotic disorder.

Co-occurring substance use and recent-onset mood or psychotic disorder: A clinical dilemma
Presentation of concomitant substance use and mood or psychotic disorder frequently poses a clinical dilemma, especially during the earlier stages of the illness when the longitudinal trajectory of the illness is virtually unknown. On the one hand, mood and psychotic disorders are known risk factors for developing SUD [13, 14]. On the other hand, many recreational substances have mood-altering and/or psychotomimetic properties [15, 16]. In theory, determining the nature of the relationship between substance use and psychopathology can help clarify the diagnosis and inform treatment planning. Several relationships can be considered for the role of substance use in concurrent presentations (Table 1). The first three relationship categories outlined in Table 1 assume a vulnerability for mental illness that is independent or partially independent of substance use, while the last three categories indicate the primacy of substance use.

There is, understandably, widespread concern about the potential for substance use to trigger chronic mental illness (the causal-chronic relationship in Table 1), as substance use can be seen as a crucial modifiable risk factor. Cannabis...
Correlational population-based studies in Denmark and Finland found that just under half of individuals diagnosed with cannabis induced psychosis would go on to develop schizophrenia spectrum disorders. However, it is important to recognize that the vast majority of individuals smoking cannabis do not develop psychotic episodes. Global survey data estimates that cannabis-associated psychotic symptoms requiring emergency medical treatment occur in about 1 of 200 people who use cannabis [20]. Of note, the relative risk for cannabis associated psychotic symptoms was much greater for individuals under the age of 21 (relative risk (RR) = 2.66) or diagnosed with a psychotic disorder (RR=14.01), bipolar disorder (RR = 4.30), anxiety (RR = 2.92), and depression (2.92). Reassuringly, over the 20th century in Australia, the observation of a steep rise in the prevalence of cannabis use at younger ages was not associated with a rise in the incidence of schizophrenia. [21].

Moreover, regarding the ‘chronic-casual’ relationship, studies that integrate familial and genetic risk factors suggest that this causal relationship is unlikely in schizophrenia and cannabis use [22–24]. In contrast to the Danish and Finish studies cited above, the incorporation of family history data in a more recent Swedish population study offered some insight into the intrinsic predisposition for schizophrenia amongst those with cannabis-induced psychotic disorder; this study re-iterated that cannabis-induced psychosis had the highest risk for later conversion to schizophrenia (compared to psychosis induced by other substances), but when familial risk for non-affective psychosis was controlled for in multivariate analyses, cannabis use no longer predicted an elevated risk of schizophrenia. In other words, the association between cannabis use and schizophrenia was better accounted for by a shared familial or genetic predisposition for both rather than the direct effects of cannabis alone [23]. This is further corroborated by an older Danish population

Table 1. Possible roles of substance use in mental disorders

<table>
<thead>
<tr>
<th>Relationship category</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Coincidental: No direct causal relationship</td>
<td>The two conditions are assumed to be completely independent, or are correlated as a result of shared genetic vulnerability (i.e., horizontal pleiotropy, which refers to when a gene independently affects more than one phenotype) [26] or environmental risk factors.</td>
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<td>2. Consequential: Reverse causation or substance use as consequence</td>
<td>Substance use is conceptualized as a form of self-medication (e.g., depression leading to alcohol or cannabis use) or as a symptom of an independent mental disorder (e.g., a manic episode leading to high-risk behaviours including substance use).</td>
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<td>3. Contributory: Substance use as contributory</td>
<td>Substance use is a risk factor, triggering factor, or exacerbating factor that contributes to the development or deterioration of a chronic mental disorder (e.g., unmasking the illness, leading to an earlier age of onset, exacerbating the symptoms, limiting response to treatment). In this case, the clinician assumes there is an underlying mental illness, or at least a general vulnerability to a mental disorder that happened to have been triggered or exacerbated by substance use. Therefore, the presence of substance use is neither necessary nor sufficient for the developmental of mental disorder.</td>
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<tr>
<td>4. Causal - chronic: Substance-triggered chronic mental disorder</td>
<td>A chronic mood or psychotic condition, without any apparent prodrome or clinical risk factors, seems to be precipitated by substance use but persists well beyond the substance use. Therefore, substances are the necessary risk factor for revealing a predisposition for chronic mental illness. In genetic association studies, this is referred to as vertical pleiotropy, i.e., when a gene affects one phenotype (substance use) that then affects another downstream phenotype (chronic mental disorder) [26].</td>
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<td>5. Causal - sub-acute: Substance-induced mental disorder</td>
<td>Sub-acute mood or psychotic episodes only occur in the presence of substance use (as per DSM-5-TR criteria for substance-induced mental disorders). Therefore, substance use is a necessary cause of the psychiatric presentation but does not cause a chronic illness that persists well beyond the physiological effect of the substance. In other words, the clinician assumes that the patient has a specific vulnerability to the effects of a substance, as opposed to a general vulnerably to having a mental disorder (#3).</td>
</tr>
<tr>
<td>6. Causal - acute: Substance intoxication or withdrawal</td>
<td>Substance use can mimic mood or psychotic disorders (e.g., cannabis intoxication can lead to brief paranoid thoughts and cocaine withdrawal has an overlap with depressive symptomatology). In this case, substance use is a sufficient cause of only the acute presentation, and no underlying vulnerability is assumed.</td>
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study that also incorporated familial data, in which the authors felt that cannabis-induced psychosis should be treated as an early sign of schizophrenia [24].

Furthermore, a European genome-wide association study (GWAS) found strong evidence that the same genetic changes that predispose individuals to cannabis use disorder also predispose schizophrenia, i.e., horizontal pleiotropy (relationship 1, Table 1). In contrast, evidence for a model of vertical pleiotropy, e.g. genes increase the risk for cannabis use disorder and then consequently schizophrenia (or the reverse), was mixed [22]. Similarly, GWAS data investigating the link between other substance use and independent mood or psychotic disorders also conclude horizontal pleiotropy [26].

Altogether, current studies do not support that the ‘causal-chronic’ relationship category commonly accounts for concurrent disorders. Thus, we hold that treatment plans for chronic mood or psychotic disorders in the context of substance use should generally follow the same principle as treating concurrent conditions in the context of the first three relationship categories (coincidental, consequential, or contributory). That is, interventions should focus on both the mood or psychotic disorder as well as moderation of substance use.

Conversely, if mood and/or psychotic symptomatology is fully attributed to the physiological effects of an exogenous substance (categories 5 and 6), maintenance treatment with psychotropic medications (which have the potential to cause serious side effects) may not be routinely indicated; instead, the recommendation would be to focus on substance use interventions. If despite counselling, the youth remain pre-contemplative about moderating their substance use, then off-label use of psychotropics to target secondary mood or psychotic symptoms can be considered explicitly as a means of harm-reduction. However, emphasis should remain on addressing the primary risk factors; in most cases, this includes the social determinants of health that may perpetuate harmful substance use.

The above classification can provide a conceptual framework to facilitate clinical decision making with the hope of avoiding both under-recognition/under-treatment and over-diagnosis/over-treatment of mental disorders. However, in clinical practice making such distinctions (especially during early presentations) proves to be difficult if not impossible for the following reasons:

a) Limited cross-sectional differentiation: Efforts have been made to develop strategies to differentiate between substance-induced and early stages of a independent psychotic disorder [27]. However, as demonstrated in a recently published systematic review [28], there is no reliable way to make such distinction, especially in the absence of longitudinal data. Similarly, patients with concurrent major depressive disorder (MDD) and SUD have been shown to be indistinguishable from those with substance-induced depression based on patterns of comorbidity and risk factors [27].

b) Common outcomes: Accumulating evidence from cohort studies indicates that the diagnosis of substance-induce psychosis is a major risk factor for independent psychotic and bipolar disorder. In a recent Danish registry study 32.2% of patients with substance-induced psychosis (N=6,788) converted to either bipolar or schizophrenia-spectrum disorders. The highest rate of conversion was for cannabis-induced psychosis (47.4%) [19]. Consistent with the findings of this study, a meta-analysis which included 25 studies of substance-induced psychosis estimated the overall rate of transitioning to schizophrenia to be 25%, with cannabis-induced psychosis being the strongest predictor of transition at 34% [29]. Importantly, the pooled rate of transition to schizophrenia for substance-induced psychoses was similar to brief and atypical psychoses that were not substance-induced. The authors concluded that “the treatment of psychoses induced by cannabis, amphetamines, and hallucinogens should be considered within the same framework of assertive early psychosis intervention as for other brief psychotic disorders” [29 p. 512]. Similarly, in a prospective study of patients with baseline diagnoses of substance -induced and -independent depression, most patients received the diagnosis of independent depression after 12 months, regardless of their baseline diagnosis [30].

c) Limitations in reviewing temporal relationships: One can argue that by examining the temporal relationship between the onset of substance use and manifestation of the psychiatric disorder, we can establish which condition led to the other. First, this argument assumes a unidirectional relationship between substance use and psychiatric conditions. However, there is plenty of evidence indicating that substance use and psychopathology may trigger, maintain, and exacerbate each other [31]. Second, many patients may not be able to provide accurate information regarding the exact timeline of their substance use and psychiatric symptoms. Third, development of both substance use and psychotic disorders is frequently insidious/gradual, which makes it even harder to know which one preceded the other. Finally, the post hoc ergo propter hoc fallacy: even if we assume a unidirectional causal relationship
between substance use and psychopathology, and we have access to accurate and reliable patient information, a mere temporal succession of two phenomena does not prove one caused the other.

d) Disease staging: During the early stages of mood and psychotic disorders, symptoms may be more transient and milder [32, 33]. Overt symptoms may only become apparent once there is a trigger such as substance use or upstream stressors that prompt substance use, therefore appearing to be substance-induced. However, as the illness progresses to the next stages, the symptoms may become more persistent and may not need to be triggered by substances. In the absence of longitudinal monitoring, it is virtually impossible to distinguish between the early stages of a bona fide psychiatric illness and a self-limiting substance-induced condition.

e) Polysubstance use: Identifying causal relationships between concurrent disorders is further complicated by the concurrent use of multiple substances.

Altogether, the above challenges obscure the clinician’s ability to identify which causal relationship accounts for the associations between substance use and the mood or psychotic symptoms experienced by any given patient. This is especially true on a cross-sectional encounter. Instead, they may rely on heuristics to inform their clinical decision making.

The role of heuristics and cognitive biases in clinical decision making

The importance of heuristics in clinical decision making remains an active area of study since the pivotal publication by Tversky & Kahneman [34, 35]. Heuristics are colloquially known as “rules of thumb” or “mental shortcuts”, referring to efficient evaluation strategies for problems with incomplete data, usually because of resource constraints including time constraints. The trade-off in a gain of efficiency is an increased risk of cognitive bias and in the clinical setting, diagnostic error [36]. Since there is an element of uncertainty in most stages of clinical decision making, from diagnosis through evaluation of individualized treatment, physicians commonly use heuristics in their clinical decisions. However, while these heuristics may improve clinical efficiency, it is important to recognize when and how these may systematically bias clinical decision making. Examples of common heuristics and cognitive biases that can affect clinical decision making include:

- **Availability heuristic**: tendency to use information that comes to mind easily such as precipitants rather than predisposing factors. Similarly, the *Post hoc ergo propter hoc* fallacy (“after this therefore because of this”).
- **Jumping to conclusions**: cross-sectionally, this may lead to favouring acute or sub-acute diagnoses as chronic conditions may require more time to diagnose.
- **Fallacy of the single cause**: causal oversimplification may favour against comorbid diagnoses.
- **Ambiguity aversion**: objective lab tests such as drug tests may carry more weight than subjective recall.
- **Anchoring bias or diagnostic momentum**: accepting a previous diagnosis without critical review.
- **Outcome bias**: favouring diagnoses that are more readily modifiable or lead to better outcomes

Many of these biases tend to favour the primacy of substance use in early presentations of psychiatric disorder, which in turn can contribute to the under-recognition and under-treatment of potentially serious, yet treatable mental health conditions. To our knowledge, there is no published data that could test this hypothesis (let alone data specific to the adolescent population), and this would likely vary greatly according to regional practices. This proposed set of biases do not suggest that the clinician should compensate by uncritically favouring independent mood or psychotic disorders, as over-diagnoses of these conditions carries the risks of inappropriate treatment. It is also crucial to consider how the referral setting can bias diagnostic consideration, e.g., assessing patients in the emergency department versus specialist psychosis or mood clinics.

Conclusion and recommendations for clinicians

Substance use is highly prevalent among youth who present with early psychosis or mood disorders. This can lead to diagnostic uncertainty since, in the absence of longitudinal monitoring, clinicians may not reliably differentiate between an early presentation of an independent mental disorder and a self-limiting substance induced condition. Moreover, prospective studies suggest that many patients whose early presentations of mood or psychotic disorder were initially attributed to the effects of substances will go on to develop independent mental illnesses. Ultimately, for any individual patient with concurrent disorders, it is often difficult to determine with any certainty whether chronic psychiatric illness was directly caused by a exposure to a substance, whether substance use was coincidental or a consequence of underlying chronic illness, or whether
substance use triggered or exacerbated vulnerability for a chronic psychiatric illness.

Since diagnostic uncertainty is inherent during the early presentation of comorbid substance use and mood or psychotic disorder, clinicians tend to use heuristics which are linked to cognitive biases and can lead to premature diagnostic closure. Unfortunately, this can result in a missed critical window of opportunity for early intervention, as the duration of untreated illness is a major modifiable factor in the prognosis of both mood and psychotic disorders [37, 38]. In view of the above arguments, we would like to offer the following reminders and recommendations for clinicians who care for individuals with early presentation of mood or psychotic disorder and concomitant substance use:

- Above all, as clinicians, we need to embrace uncertainty and cultivate clinical humility during the diagnostic process. Psychiatric diagnoses are hypotheses based on available information; and with new information comes new hypotheses.
- It is important to take detailed history of both substance use and psychiatric symptoms, obtaining collateral information (when available), and to look for evidence for psychiatric symptoms (including subthreshold symptoms) prior to the onset of substance use or during periods of abstinence.
- Assessment should include a detailed review of developmental, social, and academic histories to contextualize the presenting symptoms, their severity, and their persistence by considering the complex interplay between both intrinsic (e.g., biological vulnerabilities) and extrinsic (e.g., psychosocial stressors, substance use) factors.
- If the patient presents with a syndromal mood or psychotic disorder, we recommend erring on favouring an independent psychiatric disorder (with strong encouragement of psychiatric follow-ups and if indicated, treatment) until additional information suggests otherwise. Crucially, this approach mitigates the risk of an early period of untreated illness.
- If, on the other hand, the patient presents with subsyndromal or self-limiting symptoms of a mood or psychotic disorder, our recommendation is to consider the possibility of a prodromal phase/early stage of a psychiatric illness and therefore to provide psychoeducation to the patient and their family and to offer follow-up.
- It is often necessary to treat both conditions (SUD and other psychiatric disorders) simultaneously to achieve the best possible clinical outcome.

Regarding the clinical vignette above, the patient meets the diagnostic criteria for brief psychotic disorder and cannabis use disorder. We would provide a multifactorial explanation to account for the emergence of psychotic symptoms including an underlying vulnerability to psychosis that is possibly exacerbated by substance use or psychosocial stressors. We would emphasize the positive prognostic factors but also acknowledge the uncertainty regarding long-term outcomes.

Finally, we would strongly recommend an outpatient follow-up, preferably through a specialized early intervention program, for provision of ongoing psychiatric monitoring, psychoeducation, and substance use counselling, as well as psychotherapy, and pharmacotherapy as indicated.

We hope this article promotes a dialogue among clinicians regarding the complexities involved in the assessment and management of early presentation of mood and psychotic disorders.

**Conflicts of interest**

Dr. Keramatian is supported as a health professional investigator by Michael Smith Health Research BC, Vancouver Coastal Health Research Institute and VGH & UBC Hospital Foundation. He has previously served on the scientific advisory board of AbbVie.

**References**