Impact of Substance Use Disorder on Presentation of Schizophrenia

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Abstract

Background: The co-morbidity of substance abuse and schizophrenia is very high and apart from its etiological influence, this affects phenomenology, course and outcome of each other. These can include onset, course, and association of mood, hostility, anxiety, and severity of symptoms, relapses, and frequent hospitalizations, non-compliance to treatment and poorer psychosocial functioning.

Methods: The literature (Medline, Psycinfo, Scopus, and Cochrane Database of Systematic Reviews, Google scholar, Index Copernicus International and Pro Quest medical databases) on comorbid substance use and schizophrenia was reviewed.

Results: This review presents recent understanding of this co-morbidity, addressing substance use as risk factor and impact on onset for schizophrenia and its early influence over positive, negative or cognitive symptoms dimensions. Individual class of substance of abuse and various other influential factors such as duration of untreated psychosis, treatment course and mortality are related directly or indirectly.

Conclusion: Overall the co-morbidity of substance abuse and schizophrenia causes diagnostic instability, resulting in poor functional outcome; thus needs better awareness and understandings for its prevention, assessment and treatment.

Keywords: Substance use disorder; Schizophrenia; Presentation of symptoms

Introduction

About half of the patients diagnosed with schizophrenia have comorbid substance use disorders [1-3]. Although it has been suggested that- an important contributor to better outcome in schizophrenia in developing countries like India is low substance use comorbidity [4,5], some studies have found prevalence up to 54% in India [6,7]. More importantly, prevalence is even higher and reaches up to 75% in patients with first-episode psychosis [8]. A recent meta-analysis showed that patients continue to have this comorbidity and odds of continued cannabis use between 6 months and 10 years following first episode psychosis is 0.56 [9]. Many studies have described the long term course and outcome of comorbid schizophrenia and substance use disorders. They highlight that patients of schizophrenia with comorbid substance use have poorer compliance, frequent psychotic relapses and hospitalizations [10]. This review comprises of an overview about the impact of substance use on acute course of schizophrenia.

Method

We searched medline, psycinfo, scopus, Cochrane Database of Systematic Reviews, Google scholar Index Copernicus International and Pro Quest medical databases for available full length articles (English). We also included other language articles whose abstracts were available in English. Articles on schizophrenia (keywords: schizophrenia, schizophrenic form, first episode psychosis, early psychosis, recent onset schizophrenia, acute course in schizophrenia, short term schizophrenia) and substance use disorders (keywords: substance [abuse, dependence, use disorder] drug, alcohol, cannabis, cocaine, opiates, stimulants, tobacco) and short term course [keywords: course, short term course, acute course, presentation, short term presentation, acute presentation] were searched for. A total of 2136 articles were returned for different combination searches and across various search engines. Abstracts of the articles were initially read to screen them. About 85% of the articles were deemed ‘not relevant’ to the current subject. We included original (full length, brief) and review (systematic, selected) articles that were relevant to the present specific research question. Recently published articles, preferably review articles were chosen over older ones; many cross references were also checked and articles found. Finally we ‘selected’ a
total of 64 articles that focused on or had data on influence of substance on acute/short term presentation of schizophrenia.

Table 1 provides a list of all the reviews selected for the present review. Also mentioned is the aspect of emphasis of each review.

Table 2 provides a list of research articles, which particularly aimed at studying impact of substance use disorders on clinical presentation of schizophrenia, selected for the present review. The details on the diagnostic population, type of substance use disorder studied, source of the included sample, the research design and limitations of each of these respective studies are also given.

### Table 1: List of reviews selected

| S.no | Study                                | Topic                                                                 | Particular emphasis                      |
|------|--------------------------------------|-----------------------------------------------------------------------|------------------------------------------|
| 01   | Bagot et al. [38]                    | Adolescent Initiation of Cannabis Use and Early-Onset Psychosis       | Adolescent Initiation                    |
| 02   | Horsfall et al. [69]                 | Psychosocial treatments for comorbid severe mental illnesses and substance use disorders | Psychosocial treatments                  |
| 03   | Kerner [58]                          | Comorbid substance use disorders in schizophrenia                     | A latent class approach                  |
| 04   | Koskinen et al. [1]                  | Prevalence of alcohol use disorders in schizophrenia                  | Prevalence                               |
| 05   | Koskinen et al. [2]                  | Rate of cannabis use disorders in clinical samples of patients with schizophrenia | Prevalence                               |
| 06   | Kraan et al. [39]                    | Cannabis use and transition to psychosis in individuals at ultra-high risk | Individuals at ultra-high risk           |
| 07   | Le Bec et al. [22]                   | Cannabis and psychosis: search of a causal link                       | Etiological models                       |
| 08   | McLoughlin et al. [64]               | Cannabis and schizophrenia                                            | Comprehensive                           |
| 09   | Meister et al. [8]                   | Dual diagnosis psychosis and substance use disorders in adolescents  | Adolescents                              |
| 10   | Myles et al. [9]                     | Cannabis use in first episode psychosis                               | Prevalence, time course of further use   |
| 11   | Myles et al. [30]                    | Cannabis use and earlier age at onset of schizophrenia and other psychoses | Confounding factors                      |
| 12   | San et al. [67]                      | Treatment of schizophrenic patients with substance abuse disorders   | Antipsychotic treatment                  |
| 13   | Thoma et al. [56]                    | Comorbid substance use disorder in schizophrenia                      | neurobiological and cognitive underpinnings |
| 14   | Tucker [57]                          | Substance misuse and early psychosis                                  | An additional emphasis on stimulant drugs |
| 15   | Verdoux et al. [60]                  | Impact of substance use on the onset and course of early psychosis    | dose-response relationship               |
| 16   | Wilkinson et al. [32,36]             | Impact of cannabis on the development of psychotic disorders         | temporal relationship, dose-response, and biological plausibility |
| 17   | Wisdom et al. [62]                   | Substance use disorder among people with first-episode psychosis      | Course and treatment                     |

### Table 2: List of Original articles selected

| S.no | Study                                | Population            | Substance | Source of sample | Study design | Limitations                                      |
|------|--------------------------------------|-----------------------|-----------|------------------|--------------|--------------------------------------------------|
| 1    | Aich et al. [6]                      | Schizophrenia         | Any       | Tertiary mental hospital | Compared patients with and without substance use | Small sample; cross sectional design; only inpatients |
| 2    | Allegri et al. [28]                  | First episode psychosis | Any       | Community mental health centers | 8 year follow up study | Sample size of specific drug groups small       |
| 3    | Andreasonson et al. [14]             | Conscripts            | Cannabis  | Registry         | 15-year follow-study with a sample size of 45,570 | -                                               |
| 4    | Arsenault et al. [15]                | general population birth cohort of 1037 | Cannabis  | Registry         | Comparison of groups varying in age of onset of cannabis use | Self-report assessment Retrospective assessment |
| Study ID | Authors | Diagnosis | Intervention | Follow-up | Design |
|----------|---------|-----------|--------------|-----------|--------|
| 5 | Barrowclough et al. [37] | Recent onset psychosis | Cannabis | Early Intervention Services | 18 month follow-up study | Insufficient statistical power |
| 6 | Bersani et al. [23] | Chronic schizophrenia | Cannabis | NA | Cross-sectional comparative design | Only males; small sample |
| 7 | Broussard et al. [47] | First episode psychosis patients | Any | Inpatient psychiatry hospital | Cross sectional prediction design | Only inpatients; Small sample |
| 8 | Bühl er et al. [24] | First episode schizophrenia | Any | General population | Both retrospective and prospective | Retrospective assessment of psychosis onset |
| 9 | Camchong et al. [42] | Treatment seeker for cannabis use disorder | Cannabis | Outpatient department | 18 month Longitudinal assessment of resting functional connectivity | |
| 10 | Caton et al. [48] | Primary psychotic disorders with concurrent substance use and substance-induced psychoses | Any | Psychiatric emergency department admissions | 3 year longitudinal study comparing primary psychotic disorders with concurrent substance use and substance-induced psychoses | |
| 11 | Caton et al. [65] | -do- | -do- | -do- | 1 year longitudinal study to assess predictors of relapse | |
| 12 | Caton et al. [50] | -do- | -do- | -do- | 1 year longitudinal study to assess diagnostic stability in the two groups | |
| 13 | Caton et al. [35] | -do- | -do- | -do- | 2 year longitudinal study comparing primary psychotic disorders with concurrent substance use and substance-induced psychoses (esp. gender) | |
| 14 | Chakraborty et al. [55] | Schizophrenia | Any | Tertiary mental hospital | Compared and followed up patients with and without substance use | Smaller sample; shorter follow-up |
| 15 | Dekker et al. [29] | Non-affective psychosis | Any | NA | Correlational | Retrospective analysis |
| 16 | Ferdinand et al. [16] | General population | Cannabis | Registry | A 14-year follow-up study | ‘Psychotic symptoms’ not psychosis assessed |
| 17 | Fergusso et al., [17] | General population cohort | Cannabis | Birth registry | A 25-year longitudinal study | |
| 18 | Fraser et al. [49] | First episode psychosis | Any | Psychiatric inpatient service | Comparing substance induced and primary psychotic disorders with concurrent substance use | Small sample |
| 19 | González-Ortega et al. [61] | First episode psychosis | Cannabis | Psychiatric inpatient service | 5 year follow-up study | Small sample |
| 20 | Henquet et al. [18] | Young people with and without predisposition for psychosis | Any | Population based sample | 4 year follow-up study | |
| 21 | Hjorthøj et al. [66] | Schizophrenia, bipolar disorder, or unipolar depression | Any | Register-based cohort | Prospective, comparison of various diagnostic groups | |
| 22 | Kovaszny et al. [59] | Schizophrenia and 106 subjects with affective psychosis | Any | Inpatient department | 6-month longitudinal comparison | |
| 23 | Mauri et al. [26] | First episode of schizophrenia | Any | Inpatient psychiatric service | Comparative | Cross sectional design |
Why comorbid?

Comorbid substance use, also termed as ‘dual diagnosis’, has been theorized based on several models like self-medication, common or bidirectional factor or genetic vulnerability. Although the self-report literature, to an extent, supports the self-medication hypothesis, none of the hypotheses have enough empirical backup [11]. Enthusiasm regarding neurobiological basis for substance use in schizophrenia led to studies that showed frontal and hippocampal dysfunction in schizophrenia leads to disturbances in drug reward; hence suggesting that addictive behaviour as a primary disease symptom of psychosis [12]. However, replicability of these findings is also questionable.

Substance use as a risk factor for schizophrenia

Among the earlier studies, Tien and Anthony [13] found that alcohol use has been associated with risk of developing schizophrenia. Similarly, in a landmark study Andreasen et al. [14], found that cannabis consumption is an independent risk factor for schizophrenia. They found a relative risk for developing schizophrenia among cannabis users compared to non-users was six. Recent literature however reveals that evidence to suggest that substance use may have a causal role in the development of psychopathology is limited to cannabis and not for other substances [11]. Both longitudinal [14-20] and experimental [21] studies have shown that cannabinoids consumption is a definite risk for developing schizophrenia like psychosis. A systematic review found a clear dose-effect relationship between cannabis use and the emergence of psychosis [22]. Regarding other psychoactive substances it has been argued that although alcohol dependence is predictive of psychotic experiences, it (per se) does not cause psychosis. Similarly, although a brief amphetamine-induced psychosis is well documented, the contribution of amphetamine ‘causing’ schizophrenia per se is dubious. Research on cocaine and opiates as a risk factor for schizophrenia is very limited indeed [11].

Impact on onset

In more than 60% of patients diagnosed with comorbid substance use disorder (predominantly cannabis) along with schizophrenia the onset of substance use is before the onset of illness [23-27]. A recent meta-analysis showed that interval between initiation of regular cannabis use and age at onset of psychosis was 6.3 years [9]. Amongst various substances of abuse, cannabis has been found to be associated with an earlier onset of psychosis compared to other drugs/substances [28]. One study found that substance abuse onset and illness onset occurred highly significantly within the same month [24]. This is more specific to cannabis users; in nearly two-thirds of cannabis-using patients, age at most intense cannabis use proceeded the age at onset of first psychosis [29].

Importantly, age at onset of schizophrenia has been found to be nearly 2-3 years earlier in patients with comorbid cannabis...
use disorders compared to non-users, after controlling for various confounding factors [29,30]. Among first episode schizophrenia patients, about three-fourths of cannabis users had the onset of cannabis abuse before the onset of positive symptoms [31]. Further, it has been recently claimed that age at onset of cannabis use moderates the link between cannabis and psychosis, especially schizophrenia [32]. However, it is important to note here that younger age at presentation has been found to be ‘not significantly’ associated with positive symptoms, negative symptoms and daily functioning [33]. Also, no associations between age at onset and regional grey matter volumes have been found [34]. An important factor related to earlier onset of both substance use and psychosis is increased genetic vulnerability [23,27]. Interestingly, in the subset of patients with comorbid substance use disorder, males have an earlier age of onset than females [29,35].

Cannabis use in adolescents and subsequent risk of schizophrenia

Discussing Cannabis use in adolescents and subsequent risk of developing psychosis is of special importance. Studies have suggested that cannabis use during adolescence is associated with a higher risk of developing psychosis in adulthood; this risk declines when use is later and the association between cannabis-use during adolescence and risk of psychosis is dose-dependent [36]. A recent longitudinal study on the impact of cannabis use on clinical outcomes in recent onset psychosis reports that greater dose of cannabis is related with higher depression and anxiety. This study also found that later reductions in cannabis use are associated with improved patient functioning [37]. Another study observed that initiation of cannabis use during adolescence is associated with psychotic symptoms (onset, severity as well as related functional impairment) in a dose-dependent pattern [38]. A recent systematic review and metaanalysis, suggests a tentative dose-response relationship between current cannabis use and transition to psychosis. This study further emphasizes that only cannabis abuse or dependence is predictive of transition to psychosis in ultra-high risk individuals [39].

A recent review on cannabis and adolescent brain development, suggest that synaptic pruning and white matter development as two processes that are harmfully affected by cannabis use in adolescence and, impairments in these processes underpin the cognitive and emotional deficits related to cannabis use during adolescence [40]. Further, cannabis use was related to reduce gyration in the prefrontal cortex, which in turn is implicated in several cognitive functions [41]. Reduced functional connectivity between caudal anterior cingulated cortex and dorsolateral and orbitofrontal cortices, found in adolescent cannabis users over time, has been found to predict higher amounts of use and impaired cognitive functioning [42]. Cognitive dysfunction has been found to moderate the associations between cannabis use and vulnerability to subsequent psychiatric morbidity [43]. Preliminary evidence also suggests that males and females might have distinct neurocognitive vulnerabilities for cannabis use in young adults [44].

Impact on duration of untreated psychosis

A systematic review and meta-analysis inferred an association between shorter duration of untreated psychosis and cannabis use in first episode psychosis patients. This review further suggests that this statement refers to ‘use’ in terms of current or recent use [45]. However, having ever used cannabis (lifetime use) and the amount of alcohol use were significantly associated with longer duration of untreated psychosis [46-47].

Substance and psychopathology

Presence of visual hallucinations, higher levels of insight, more severe hostility and anxiety symptoms are important factors that discriminate patients with substance induce psychosis from primary schizophrenia comorbid with substance use disorders [48,49]. However, it is found that within one year the diagnosis, substance induced psychosis loses its stability and 25% of them are diagnosed with schizophrenia [50,41]. Indeed recent findings also suggest that cannabis disorders, more than other substances, predict an increased likelihood, over 2-5 years, of progression to schizophrenia [51].

Positive symptoms

There is fair bit of heterogeneity in the findings on positive symptoms. While several studies show a significantly increased severity of positive symptoms [23,24,26,31,46,52] in schizophrenia patients with substance use disorder, some studies have found that these patients have significantly lower positive symptoms [53] and some have shown a lack of significant difference between schizophrenia patients with substance use and non-use [27,54]. This heterogeneity may be explained by variations in the onset of substance use and psychotic episode. It has been reported that patients whose onset of schizophrenia preceded the beginning of substance abuse had more positive symptoms [23]. Analyzing the sub scores of positive symptoms further, found that substance, especially cannabis; abusers have higher “thought disturbance” and “hostility” scores. Significantly, higher hostility scores were found in patients using cocaine and poly-substance; suggesting that use of other substances might also have an influence on this heterogeneity [26]. Moreover, patients showing greater positive symptoms were poly-substance abusers [23]. Pertinent to mention here is that among poly-substance abusers, cannabis (49%) is mostly used followed by alcohol (13%), and cocaine (4%) [26].

Negative symptoms

Although some studies showed no significant difference between schizophrenia patients with substance use and non-use [53], most studies have found that comorbid substance use disorder in schizophrenia is associated with lower and less severe negative symptoms [23,24,46,54]. However, significantly increased severity of depression [52,55] manic [52] and anxiety [53] scores were also found in this sub set of patients. Women were found to have greater depression than men [35].
Cognitive symptoms

A few brief-selected reviews [56,57] infer that neurocognitive function might be less disrupted in substance-abusing compared to non-abusing schizophrenia patients. However, some studies have highlighted dysfunction in abstract thinking to be present in dual diagnosis patients at short treatment follow-ups [55].

General functioning

Over all, using a ‘latent class approach’, it has been claimed that substance use comorbidity is associated with more acute symptoms and a more severe disease course and not with a specific pattern of positive and negative symptoms [58]. Short term (6-12 month longitudinal) course analysis showed that substance use, especially cannabis, is related to poorer psychosocial functioning [52,59]. Moreover it was also found that continued use of cannabis following the episode of psychosis was associated with poorer functional outcome [52,60]. Pertinently, cannabis users who abstained have the greatest improvement in symptoms at 1 year compared with continued users and non-users [33]. In depth analysis has shown that, subclinical depressive symptoms have been found to be significantly associated with continued abuse of cannabis during treatment follow-ups; hence associated with worse functioning [61]. Intriguingly, this relationship between substance use and clinical functioning is restricted to schizophrenia patients and not with those with affective psychosis [59].

Impact of a treatment course

A very few studies have investigated the impact of treatment on early or short term course of schizophrenia, especially first episode schizophrenia. A systematic review found that approximately 50% of patients become abstinent or significantly reduce their alcohol and drug use after a first episode of psychosis [62]. However, even in short term course of one year, schizophrenia patients with comorbid substance use disorders have been found to have significantly higher rate of hospitalizations (after adjusting for potential confounders) [63]. A 3-month short- longitudinal study found that 27% of first episode schizophrenia patients with comorbid substance abuse had responded to treatment compared to 35% of those without comorbid substance use. Specifically, first episode schizophrenia patients with comorbid substance use disorder were found to be less likely responders to olanzapine than those without comorbid substance use disorder, in this study [46]. A recent Cochrane review, which assessed medium term course, shows that not even one form of treatment could show superiority for reduction in cannabis use. Moreover, the meta-analysis found that improvement in psychopathology (i.e. positive and negative symptom scores) over a course of treatment was not significantly different in schizophrenia patients with comorbid substance use disorder than those without [64].

Remission and Predictors

The predictors of remission in substance using schizophrenia patients and non-users were not significantly different. Lower positive and negative symptoms at baseline, better insight, and a shorter duration of untreated psychosis predict remission in both the groups [65].

Impact on brain

Specifically in schizophrenia patients using alcohol, structural and functional brain damage is evidenced [56]. Although patients with schizophrenia with or without comorbid cannabis use disorder have smaller volumes of amygdala, putamen, insula, parahippocampus and fusiform gyrus than healthy controls, the cannabis users were found to have larger volumes of the putamen. This study speculates whether a large putamen represents a risk factor for developing cannabis use disorders [34].

Mortality

In schizophrenia, the all cause-standardised mortality ratios in those with lifetime substance use disorder have been found to be greater than in those without. This study also showed that increase risk of all-cause mortality is independent of the type of substance, single or polysubstance [66].

Treatment strategies

Factors for remission in psychotic disorders that co-occur with substance use disorders are similar to those reported previously in studies of schizophrenia- better pre-morbid adjustment, smaller duration of untreated psychosis, fair insight into psychotic symptoms, and lower severity of positive symptoms [65]. Among the treatment strategies both pharmacological and psycho-social modes have been proposed. The majority of pharmacological studies suggest the effectiveness of second-generation antipsychotics, particularly clozapine [67]. A review found no difference between risperidone and olanzapine, but clozapine had a distinct advantage in reducing psychotic symptoms as well as substance abuse (including smoking). There is some evidence of the usefulness of quetiapine in dually diagnosed patients, particularly using alcohol, cocaine and amphetamine [68]. The psycho-social treatments available for these dual diagnosis patients are motivational interviewing, relapse prevention, cognitive-behavioural therapy, case management, contingency management and skills training [69]. It has been emphasized that these treatments have to be tailored to individual needs.

Reasons for relapses

A meta-analysis of eight studies showed that the presence of a substance use disorder significantly increases the risk of poor compliance to pharmacological treatment in schizophrenia patients. Further, the meta-analysis of the risk of relapse associated with the presence of substance use disorders including only three studies concluded that having an associated substance use disorder doubles the risk of poor compliance to pharmacological treatment and this comorbidity explains a fifth of all factors involved. Further studies to develop specific
strategies to better treat patients with schizophrenia and substance use disorder are awaited [70].

Conclusion

With a high prevalence of comorbid substance use disorders in patients diagnosed with schizophrenia, these subset of patients pose a challenge in the diagnosis and treatment of schizophrenia—causing diagnostic instability to resulting in overall poor functional outcome. Intense effort is obligatory in developing interventions for substance reduction that are ably adapted for people with psychosis, especially schizophrenia.

Limitation

As the present paper is a ‘selected review’ it has inherent limitations compared to a ‘systematic review’. Several databases/studies that may be relevant could not have been included; and it lacks a systematic synthesis. Hence, we do not comment on specific study characteristics and quality of research of individual studies and, publication and related biases. Conducting future systematic reviews on the question addressed by the index study would be valuable.

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