

A 10-year retrospective study of inpatient adolescents with schizophrenia/schizoaffective disorder and substance use

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Abstract

The comorbidity of schizophrenia/schizoaffective disorder and substance use is a major psychiatric concern that is associated with aggressive and suicidal behavior. This study investigated the clinical correlates and characterizes adolescent psychotic inpatients with and without comorbid substance use. We performed a retrospective study of 188 adolescent inpatients who were admitted between the years 1994 and 2004 to the inpatient unit of Geha Mental Health Center and who were diagnosed as suffering from either schizophrenia or schizoaffective disorder. The substance-using psychotic inpatients were found to have more relatives with substance-related disorders, fewer comorbid anxiety disorders, lower scores on the Brief Psychiatric Rating Scale and Hamilton Scale for Depression, higher scores on the Overt Aggression Scale, and they were more suicidal than the nonsubstance using inpatients. Adolescent inpatients with schizophrenia and schizoaffective who use substances possess differential clinical characteristics and particular correlates that justify adopting a specific approach to this high-risk clinical subgroup.

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1. Introduction

The comorbidity of schizophrenia and substance abuse is well documented, with up to 60% of the patients being reported using or abusing illicit drugs [1–4]. The rates in inpatient settings are in the same range and are sometimes even higher [4–8].

Substance abuse among patients with schizophrenia is considered a major clinical and public health concern [9]. Apart from tobacco consumption (over 70%), the most frequently used substances are alcohol (37%), cannabis (23%), and stimulants or hallucinogens (13%) [10–13]. The abuse of most of these substances has been linked to psychotic symptom exacerbation, repeated hospitalizations, poor social functioning, homelessness, increased suicide risk, and poor response to treatment [5,14–16].

To better understand the relationship between schizophrenia and the use and abuse of substances at rates far exceeding those found in the unaffected population, several models have been proposed [9,17–20]. The etiological model hypothesizes that drug abuse is a causative factor in the development of this disease in a subgroup of patients with schizophrenia [21–24]. Alternatively, the dopamine model suggests that disturbances in the reinforcement and reward function of the dopamine-producing areas of the brain may increase the vulnerability to both schizophrenia and drug abuse in some patients [25]. A third model, the socializing effects paradigm, considers drug use by patients with schizophrenia to be interpersonally reinforcing as it renders handicapped and isolated patients' social identity and group [26]. Finally, the self-medication model suggests that patients suffering from schizophrenia may use drugs to ameliorate depression [27], negative symptoms [28], or neuroleptic-induced extrapyramidal side effects [29].

A prospective study in adults has found that substance abuse in patients with schizophrenia is associated with suicidality and impulsivity, but the data collected revealed

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no correlation with scores on the Chapman Physical Anhedonia Scale, the Positive and Negative Syndrome Scale, the Clinical Global Improvement scores, or with treatment response and demographic variables [30]. Another recent study found that schizophrenic patients with substance use were younger, more likely to be male, had a shorter duration of illness, and had more police contact, but symptoms, service use, or social functioning were only minimally affected [31]. A schizophrenic patient's history of substance use was shown to be among the predicting factors of aggression during hospitalization [32] and has been reported to be associated with an earlier age of onset of the psychotic disorder [33,34]. Finally, a longitudinal study of adult schizophrenia and schizoaffective inpatients found that substance abuse among this group was correlated with fewer negative and positive symptoms, better sexual adjustment, worse school performance during adolescence, and greater family histories of drug abuse [5]. Cannabis, alcohol, and cocaine were the most commonly used drugs in that cohort. The authors concluded that patients with schizophrenia who abuse drugs may represent a subgroup with a different prognosis.

To the best of our knowledge, similar studies have not been performed in adolescents. The developmental phase of adolescence is regarded as a time of vulnerability to the adverse effects of misused substances upon psychological functioning [35]. Drugs and alcohol may interfere with learning, social and personal development, may aggravate preexisting emotional distress, and may lead to a progression to the use of other substances, possibly in increased doses. These implications may well be more severe in adolescent patients with schizophrenia.

A review of the literature regarding suicidality and substance abuse indicates that drug and alcohol use was found to be associated with suicidal behavior not only in adults [36,37] but also in adolescents as well [38–41]. Schizophrenia by itself is associated with an increased rate of suicidality; thus, substance use in these patients is expected to further increase the risk of potentially lethal self-injurious behavior. We have been unable to find a comprehensive study on the effect of substance use on suicidal behavior among adolescent inpatients with schizophrenia.

The issue of the underrecognition of substance use and abuse by medical staff has been dealt with previously [42,43]. For example, it has been noted recently that although substance misuse is very common in psychiatric patients [3], most patients were not questioned about such behavior by admitting psychiatrists [44]. General physicians were reported long ago to be poor at taking substance use and abuse histories and alcohol history in many clinical settings [45]. This finding emphasizes the importance of obtaining more data on the clinical features of substance-using and substance-misusing adolescent patients.

1.1. Aims of the study

We performed a retrospective study of inpatient adolescents with schizophrenia and schizoaffective disorder. The

goal of this study was to identify the clinical correlates and to characterize adolescent psychotic inpatients with and without comorbid substance use.

2. Materials and methods

2.1. Subjects

The sample consisted of 188 adolescents diagnosed with either schizophrenia or schizoaffective disorder. All patients admitted to the adolescent inpatient unit at a university-affiliated mental health center in Israel between the years 1994 and 2004 were included unless the duration of their hospitalization was less than 5 days. The reason for this exclusion was a dearth of clinical and anamnesis data on these patients. During this 10-year period, there were no changes in the hospital's review criteria for admission, which could have influenced or confounded the distribution of patients admitted to the adolescent inpatient unit. The study was approved by the Mental Health Center Review Board. The need for informed consent was waived by the board because the study was based in its entirety upon analyses of retrospective data obtained from medical records.

The mean age of the subjects was 17.43 years (range, 12.61–23.21 years; SD = 1.71). The mean age of their first psychiatric hospitalization was 16.72 years (SD = 1.88). One hundred twenty-four (65.96%) subjects were males. The median number of previous hospitalizations was 1, and the mean duration of hospitalization was 147.1 days (SD = 160.95). Forty-six subjects (24.47%) had been hospitalized against their will under the Mental Health Act.

2.2. Measures

Relevant clinical data were collected from the hospital's computerized medical records available beginning in 1994. These medical records were designed to contain fields that must be completed by the psychiatrist at admission and during hospitalization, thus preventing the loss of valuable data regarding the history and the current status of the patient.

Diagnoses were based on *DSM-IV* criteria [46] using data that had been collected during extensive clinical interviews performed by certified child psychiatrists, daily observations by nursing staff, and clinical team discussions led by the unit director (AA); consensus diagnosis procedures were also used to obtain diagnostic accuracy. Axis II diagnoses were assessed using the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID II, version 2.0) for every subject at 14 years or older [47].

Dosages for antipsychotic agents were converted into defined daily dose (DDD), which is the average maintenance dosage as defined by the WHO Collaborating Center for Drug Statistics [48]. For example, the DDD for perphenazine is 30 mg and for haloperidol is 8 mg.

Patients were evaluated at admission and discharged using the Brief Psychiatric Reporting Scale (BPRS) [49] and

Table 1
Demographic, familial, and diagnostic data of adolescent inpatients with psychotic disorders

	Nonsubstance users (n = 135)	Substance users (n = 53)	Statistics	P
Age, mean (SD), y	17.3 (1.8)	17.7 (1.4)	F = 2.2, df = 186	.15
Age at first psychiatric admission, mean (SD), y	16.6 (2.1)	17.1 (1.3)	F = 2.0, df = 186	.16
Male	86 (63.7)	38 (71.7)	$\chi^2 = 1.1$, df = 1	.3
Patients with first-degree relatives with schizophrenia or schizoaffective disorder	37/93 (39.8)	14/37 (37.8)	$\chi^2 = 0.00$, df = 1	.99
Patients with first-degree relatives with mood disorders	21/89 (23.6)	9/33 (27.3)	$\chi^2 = 0.03$, df = 1	.85
Patients with first-degree relatives with substance-related disorders	3/88 (3.4)	7/30 (23.3)	Fisher exact test, OR = 8.6, 95% CI = 2.1-36.0	.0025 ^a
Patients with comorbid mood disorders diagnoses	9 (6.7)	3 (5.7)	$\chi^2 = 0.1$, df = 1	.8
Patients with comorbid anxiety disorders diagnoses	15 (11.1)	0 (0)	Fisher exact test, OR = 13.7, 95% CI = 0.81-234	.007 ^a

Values are presented as number (percent) unless otherwise indicated.

^a Significant after Bonferroni adjustment.

the Hamilton Depression Scale (HAM-D) [50]. Aggression was measured by the Overt Aggression Scale (OAS) [51]. Each of these measures was and continues to be a part of the routine clinical evaluation process on this unit. Some patients were not cooperative; therefore, some of the rating scales were completed for part of the sample only.

2.3. Data analysis

The data were analyzed using the SPSS statistical package, Version 11 for Windows (SPSS, Inc, Chicago, Ill). Two-way analysis of variance, Mann-Whitney test, χ^2 with Yates correction, and Fisher exact test were used as appropriate. Logistic regression was performed to predict the probability of each psychotic patient to be a substance user versus a nonuser. Bonferroni adjustment was used to correct for multiple testing. All tests were 2-tailed.

3. Results

Of the 188 adolescent inpatients diagnosed with either schizophrenia or schizoaffective disorder who were included in the study, 53 (28.2%) were substance users. As shown in Table 1, there were no differences in age, age at first psychiatric admission, or sex distribution between the group of substance users and the nonusers. The groups also did not differ in ethnic origin distribution (data not shown).

Cannabis was the most frequently used substance, which was consumed by 44 patients (23.4%). Alcohol was used by 24 (12.7%) patients, methylene-dioxy-methylamphetamine (Ecstasy) by 24 (12.7%), lysergic acid diethylamide by 16 (8.5%), volatiles by 14 (7.4%), cocaine by 11 (5.8%), amphetamines by 9 (4.8%), and opiates by 6 (3.2%). The anticholinergic plant *Datura stramonium* (jimsonweed) was used by 2 (1.1%) patients. Thirty-five (18.6%) patients used more than one substance.

A positive family history for substance abuse (Table 1) was significantly more frequent among the substance-using patient group (Fisher exact test, $P = .0025$; odds ratio [OR], 8.6; 95% confidence interval [CI], 2.1-36.0). No difference, however, was found between the subject groups in the rates of psychotic or mood disorders among first-degree relatives. There was also no difference in the presence of additional comorbid mood disorders between the groups, but the nonusing group of patients had an elevated frequency of comorbid anxiety disorders compared with the substance-using group (11.1% vs 0%, respectively; Fisher exact test, $P = .007$; OR, 13.7; 95% CI, 0.81-234).

Table 2 presents the clinical data regarding the most recent hospitalization of the patients. The 2 groups did not differ in the number of prior admissions, the rate of involuntary hospitalizations, the length of hospitalization at the most recent admission, and the period that elapsed

Table 2
Clinical data of the most recent hospitalization of the adolescent inpatients with psychotic disorders [mean (SD) or N (%)]

	Nonsubstance users (n = 135)	Substance users (n = 53)	Statistics	P
No. of previous admissions	0.9 (1.2)	1.3 (1.9)	F = 2.4, df = 186	.13
Patients hospitalized against will, n (%)	31 (22.9)	16 (30.1)	$\chi^2 = 1.2$, df = 2	.55
Duration of the most recent hospitalization (d)	147.6 (143.3)	145.8 (200.5)	F = 0, df = 186	.94
Time until first allowed home leave (d)	30.4 (47.1)	22.7 (22.1)	F = 1.0, df = 147	.31
Antipsychotic daily dose at discharge (DDD)	1.3 (0.9)	1.3 (0.8)	F = 0.05, df = 178	.83
Anticholinergic daily dose at discharge (DDD)	0.5 (0.8)	0.5 (0.7)	F = 0.4, df = 184	.53
BPRS score at admission	50.1 (15.6)	40.7 (15.5)	F = 3.58, df = 53	.064
BPRS score at discharge	38.1 (13.5)	36.9 (17.6)	F = 0.1, df = 52	.79
HAM-D score at admission	12.8 (6.6)	6.0 (0.8)	Mann-Whitney = 88	.0093 ^a
HAM-D score at discharge	14.8 (22.3)	6.0 (4.1)	F = 0.6, df = 19	.49

Values are presented as mean (SD) unless otherwise indicated.

^a Significant after Bonferroni adjustment.

Table 3

Self-injurious and suicidal behavior during the most recent hospitalization of the adolescent inpatients with psychotic disorders

	Non-substance users (n = 135)	Substance users (n = 53)	Statistics	P
Patients with suicide ideation at admission, n (%)	31/131 (23.6)	9/50 (18)	$\chi^2 = 0.67, df = 1$.41
Patients with self-injurious behavior during hospitalization, n (%)	10/128 (7.8)	8/52 (15.4)	$\chi^2 = 2.4, df = 1$.12
OAS score at admission, mean (SD)	0.48 (1.4)	2.1 (3.1)	Mann-Whitney = 240.5	.0029 ^a
OAS score at discharge, mean (SD)	0.17 (0.62)	0.45 (1.23)	F = 1.3, df = 53	.28

^a Significant after Bonferroni adjustment.

between admission and the first allowed home visit. There were also no differences between the groups in the DDD of either antipsychotic or anticholinergic medications prescribed at discharge. The nonusing group reported depressive symptoms as assessed by HAM-D at a significantly higher rate at admission than did those of the substance-using group (Mann-Whitney, $P = .0093$). However, this difference did not persist at discharge. A similar trend ($P = .064$) was noted in psychotic symptoms measured by the BPRS; that is, the rate of such symptoms was higher among the nonusing group during admission, but this trend disappeared at discharge.

Self-injurious and suicidal behavior data are presented in Tables 3 and 4. Self-injurious behavior was reported twice as often in the substance-using group (15.4% vs 7.8%), but the difference did not reach statistical significance. Although the groups reported a similar degree of suicidal ideation at admission, it was the substance-using group that presented with a significantly higher number of previous suicide attempts per patient (0.7 vs 0.38; $\chi^2, P = .037$) and a higher rate of previous suicide attempts within the group at large (Table 4). This group also performed more suicide attempts during their most recent hospitalization (11.5% vs 6.25%; $\chi^2, P = .029$). Aggression, as measured by the OAS, was much higher in the substance-using group than in the nonusing group at the time of admission (2.1 vs 0.48; $P = .0029$) but not at discharge (Table 3).

Logistic regression analysis (using substance use as the outcome measure; age, sex, number of previous suicide attempts, presence of comorbid anxiety disorders, and family history of substance abuse as independent variables) revealed 3 variables, each of which independently predicted substance abuse among adolescent schizophrenic inpatients:

family history of substance abuse disorders (OR, 11.1; 95% CI, 2.3-52.9), past suicide attempts (OR, 1.68; 95% CI, 1.08-2.62), and age (OR, 1.28; 95% CI, 1.002-1.64). The area under the curve for these 3 variables was 0.73.

3.1. The characteristics of polysubstance users

We analyzed further the characteristics of the psychotic patients who used more than one substance (n = 35) because we believed that they represented a subclass of individuals with more prominent substance use problems. We repeated the analyses that we had previously made using the entire sample, this time comparing polysubstance users and nonusers. This second comparison did not reveal new findings, but the previous findings remained significant despite the smaller sample of this polysubstance-using group. The rate of family history of substance abuse remained significantly greater among the polysubstance-using group compared with the nonusing group (6/22 [28.3%] vs 3/88 [3.4%]; Fisher exact test, $P = .0019$; OR, 10.6; 95% CI, 2.4-46.9). The rate of comorbid anxiety disorders was higher in the nonusing group (11.1% vs 0%; Fisher exact test, $P = .043$). HAM-D scores at admission remained higher among the nonusing group (12.8 vs 6.2, respectively; Mann-Whitney, $P = .0184$), whereas/although OAS scores at admission were kept higher in the polysubstance-using group (0.49 vs 1.67, respectively; Mann-Whitney, $P = .0162$). Previous suicide attempts per patient became even more significantly higher among the polysubstance-using group compared with the nonusing group (0.94 vs 0.38, respectively; 2-tail analysis of variance, $F = 8.76, df = 166, P = .0035$).

All significant findings in the tables remained significant following Bonferroni correction (Tables 1-4).

Table 4

Distribution of psychotic patients according to the number of previous suicide attempts and the number of suicide attempts during the most recent hospitalization

	No. of suicide attempts					
	0	1	2	3	4	5
Previous suicide attempts ($\chi^2 = 11.8, df = 5, P = .037$)						
Nonsubstance users (n = 134)	101	24	5	0	3	1
Substance users (n = 51)	34	7	4	3	3	0
Suicide attempts during the most recent hospitalization ($\chi^2 = 9.0, df = 3, P = .029$)						
Nonsubstance users (n = 128)	122	3	3	0		
Substance users (n = 52)	46	4	0	2		

4. Discussion

The results support our hypothesis that adolescent inpatients with schizophrenia and schizoaffective disorder who use substances comprise a subgroup with specific clinical characteristics. This is true whether such patients are evaluated from the perspective of a psychotic disorder or from the substance use aspect.

The rate of substance use among the schizophrenic inpatients in our study (28.2%) was in the lower range reported in the literature [1–8]. This may be related to the fact that the rate of substance use among Israeli adolescents is lower than in other Western countries [52]. Data on the rates of substance use in other youth admitted to this facility with different types of psychiatric disorders are unfortunately currently not available but are estimated to be no higher than 10% (unpublished data). The relatively greater preference of adolescent schizophrenic inpatients in our study for psychomimetic drugs (cannabis, methylenedioxy-methylamphetamine, lysergic acid diethylamide, and cocaine are among the top 6) may support accumulating data indicating that patients with schizophrenia tend to prefer stimulating substances with the potential to induce psychotic symptoms rather than central nervous system depressants [5]. We attribute the use of alcohol and volatile substances in our sample to the easy accessibility, low cost, and legal status of these compounds.

The exceedingly high rate of cannabis use compared with all other substances deserves further observation. Known to have been used (smoked or eaten) for centuries for its euphoriant, psychedelic, and medicinal properties, cannabis is the most commonly abused drug among patients with schizophrenia [53]. It may be hypothesized that its popularity may be related to some of its psychiatric effects: euphoria, altered time perception, hallucinations, and dissociation of ideas [54]. Our finding that cannabis is so popular among adolescent inpatients with schizophrenia is worrisome because evidence is accumulating that its effects in adolescence may be different from that of adults, and it may be linked to depression as well [20].

An interesting finding here was the lack of a clear male/female predominance among the substance users, which is known to be characteristic of drug users [55–57]. It raises the question of the effect of schizophrenia on adolescents and the specific pathophysiology of substance use in those patients. It is plausible that schizophrenia neutralizes the sex difference that would otherwise trigger the causal factor(s) that creates the different rates of substance use between males and females reported in other populations. The findings that age, age at first admission (thought to represent the age of onset of the schizophrenic disorder), and number of previous hospitalizations did not differ between users and nonusers are consistent with studies of adult schizophrenic inpatients [5]. Similarly, the increased frequency of relatives with substance abuse among the substance-using group is not surprising, given previous studies [5,58,59]. This last

finding reiterates the important role of familial determinants in the pathogenesis of substance use that are likely to be both environmental and genetic.

We expected that the substance-using schizophrenic inpatients would show a different pattern of clinical characteristics, for instance, more previous admissions, more hospitalizations against their will, and longer admissions. However, none of these existed, supporting findings from previous adult studies [60,61]. We infer from these data that substance use in adolescent schizophrenic inpatients should be regarded differently than in conduct disorder and personality disorder patients.

The findings of lower BPRS and HAM-D scores among the substance users are rather intriguing. It may be speculated that the self-medication of psychotic and depressive symptoms is responsible for that influence, and this suggests that substance use is commonly found among such patients because the effects of these substances are reinforcing in that they help to overcome the troubling symptoms of both schizophrenia and antipsychotic treatment. Another possible explanation for this finding is that substance-using patients with schizophrenia represent a subgroup who suffers from less severe form of the disease, as has been suggested in adults [5]. It is of interest to note that although evidence indicates that the course of schizophrenia is complicated by substance abuse, patients perceive benefits from drugs of abuse [62]. Future studies, using larger samples, are needed to shed light on this important issue.

The previously reported correlation between substance use and suicidality [36–41] was demonstrated here in a sample of adolescents with schizophrenia. In addition, higher levels of aggression were measured at admission in the substance-using group, providing, therefore, another link between aggression and suicidality in this specific subset of adolescent schizophrenic inpatients. From a practical clinical aspect, this suggests that adolescent substance-using schizophrenic inpatients are at a higher risk for suicidal and aggressive behavior and should be followed with more caution. Thus, such patients require the development and implementation of specific therapeutic strategies to lessen the risk for violent and suicidal behavior. Interestingly, the elevated number of previous suicide attempts in the substance-using group was accompanied by more attempts during the most recent hospitalization but not by more suicide ideation at admission. This finding could be because of traits such as impulsivity that were not studied by us (and may play a role in both suicidality and substance use) and the effect of the closed unit on the inpatients.

4.1. Limitations

The main limitation of our study stems from its retrospective nature. Because of this approach, we were unable to collect data on the frequency and intensity of the use of the substances. It is of note, however, that a recent

study found unexpectedly high levels of detection of substance use by retrospective data pooling from the medical records as compared with the use of a structured diagnostic interview [42]. As explained earlier, our computerized records were designed in a way that would minimize such data loss. Substance use is not further defined as whether there were histories of abuse or dependence. Because of the retrospective nature of this study, we could not reconstruct accurately this information from the computerized records.

Another limitation is the potential sampling bias that has been observed in all facilities. Our facility serves a catchment area of 500,000 inhabitants, and it is the only psychiatric adolescent inpatient department in the area; therefore, this bias is considered minimal.

Finally, an absence of comorbid anxiety disorders was revealed in the substance-using group. This finding may be related to the externalizing traits of these patients or the tendency of child psychiatrists to avoid the assignment of anxiety disorder diagnoses in schizophrenic substance-using inpatients. Anxiety disorders have uncertain clinical importance in the presence of schizophrenia and schizoaffective disorders, and because it was not systematically assessed, this finding, although highly significant, should be considered with caution.

In conclusion, the findings of this study verify our hypothesis that adolescent schizophrenic inpatients who use substances possess differential clinical characteristics and certain behavioral correlates that justify adopting a specific approach toward them as a clinical subgroup. Our findings are consistent with previous reports on adult substance-using schizophrenic populations. However, they raise several key issues that need to be addressed in future prospective studies and in larger populations.

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References

- [1] Alterman AI, Erdlen FR, McLellan AT, Mann SC. Problem drinking in hospitalized schizophrenic patients. *Addict Behav* 1980;5(3):273-6.
- [2] Miller FT, Tanenbaum JH. Drug abuse in schizophrenia. *Hosp Community Psychiatry* 1989;40(8):847-9.
- [3] Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990;264(19):2511-8.
- [4] Richard ML, Liskow BI, Perry PJ. Recent psychostimulant use in hospitalized schizophrenics. *J Clin Psychiatry* 1985;46(3):79-83.
- [5] Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. *Am J Psychiatry* 1991;148(2):224-30.
- [6] Crowe DB, Rosse RB, Sheridan MJ, Deutsch SI. Substance use diagnoses and discharge patterns among psychiatric inpatients. *Hosp Community Psychiatry* 1991;42(4):403-5.
- [7] Shaner A, Khalsa ME, Roberts L, Wilkins J, Anglin D, Hsieh SC. Unrecognized cocaine use among schizophrenic patients. *Am J Psychiatry* 1993;150(5):758-62.
- [8] Lehman AF, Myers CP, Corty E, Thompson JW. Prevalence and patterns of "dual diagnosis" among psychiatric inpatients. *Compr Psychiatry* 1994;35(2):106-12.
- [9] Krystal JH, D'Souza DC, Madonick S, Petrakis IL. Toward a rational pharmacotherapy of comorbid substance abuse in schizophrenic patients. *Schizophr Res* 1999;35(Suppl):S35-S49.
- [10] Cuffel BJ, Heithoff KA, Lawson W. Correlates of patterns of substance abuse among patients with schizophrenia. *Hosp Community Psychiatry* 1993;44(3):247-51.
- [11] de Leon J, Dadvand M, Canuso C, White AO, Stanilla JK, Simpson GM. Schizophrenia and smoking: an epidemiological survey in a state hospital. *Am J Psychiatry* 1995;152(3):453-5.
- [12] Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. *Am J Psychiatry* 1992;149(9):1189-94.
- [13] Swadi H, Bobier C. Substance use disorder comorbidity among inpatient youths with psychiatric disorder. *Aust N Z J Psychiatry* 2003;37(3):294-8.
- [14] Drake RE, Osher FC, Wallach MA. Homelessness and dual diagnosis. *Am Psychol* 1991;46(11):1149-58.
- [15] Drake RE, Osher FC, Wallach MA. Alcohol use and abuse in schizophrenia. A prospective community study. *J Nerv Ment Dis* 1989;177(7):408-14.
- [16] Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry* 1994;51(4):273-9.
- [17] Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend* 2003;71(1):37-48.
- [18] Dixon L, Haas G, Weiden P, Sweeney J, Frances A. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. *Schizophr Bull* 1990;16(1):69-79.
- [19] Goswami S, Mattoo SK, Basu D, Singh G. Substance-abusing schizophrenics: do they self-medicate? *Am J Addict* 2004;13(2):139-50.
- [20] Rey JM, Martin A, Krabman P. Is the party over? Cannabis and juvenile psychiatric disorder: the past 10 years. *J Am Acad Child Adolesc Psychiatry* 2004;43(10):1194-205.
- [21] Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 2002;325(7374):1212-3.
- [22] Bowers M. The role of drugs in the production of schizophreniform psychoses and related disorders. In: Meltzer HY, editor. *Psychopharmacology: the third generation of progress*. New York: Raven Press; 1987. p. 819-23.
- [23] Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction* 2005;100(3):354-66.
- [24] Verdoux H, Sorbara F, Gindre C, Swendsen JD, van Os J. Cannabis use and dimensions of psychosis in a nonclinical population of female subjects. *Schizophr Res* 2003;59(1):77-84.
- [25] Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* 1987;237(4819):1219-23.
- [26] Millman RB, Sbriglio R. Patterns of use and psychopathology in chronic marijuana users. *Psychiatr Clin North Am* 1986;9(3):533-45.
- [27] Freed EX. Alcoholism and schizophrenia: the search for perspectives. A review. *J Stud Alcohol* 1975;36(7):853-81.
- [28] Schneier FR, Siris SG. A review of psychoactive substance use and abuse in schizophrenia. Patterns of drug choice. *J Nerv Ment Dis* 1987;175(11):641-52.

- [29] Knudsen P, Vilmar T. Cannabis and neuroleptic agents in schizophrenia. *Acta Psychiatr Scand* 1984;69(2):162–74.
- [30] Gut-Fayand A, Dervaux A, Olie JP, Loo H, Poirier MF, Krebs MO. Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity. *Psychiatry Res* 2001;102(1):65–72.
- [31] Cantwell R. Substance use and schizophrenia: effects on symptoms, social functioning and service use. *Br J Psychiatry* 2003;182:324–9.
- [32] Barlow K, Grenyer B, Ilkiw-Lavalle O. Prevalence and precipitants of aggression in psychiatric inpatient units. *Aust N Z J Psychiatry* 2000;34(6):967–74.
- [33] Green AI, Tohen MF, Hamer RM, Strakowski SM, Lieberman JA, Glick I, et al. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res* 2004;66(2-3):125–35.
- [34] Veen ND, Selten JP, van dT I, Feller WG, Hoek HW, Kahn RS. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry* 2004;161(3):501–6.
- [35] Johns A. Psychiatric effects of cannabis. *Br J Psychiatry* 2001;178:116–22.
- [36] Malone KM, Waternaux C, Haas GL, Cooper TB, Li S, Mann JJ. Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. *Am J Psychiatry* 2003;160(4):773–9.
- [37] Cornelius JR, Salloum IM, Lynch K, Clark DB, Mann JJ. Treating the substance-abusing suicidal patient. *Ann NY Acad Sci* 2001;932:78–90.
- [38] Esposito-Smythers C, Spirito A. Adolescent substance use and suicidal behavior: a review with implications for treatment research. *Alcohol Clin Exp Res* 2004;28(5 Suppl):77S–88S.
- [39] Forman EM, Berk MS, Henriques GR, Brown GK, Beck AT. History of multiple suicide attempts as a behavioral marker of severe psychopathology. *Am J Psychiatry* 2004;161(3):437–43.
- [40] Danielson CK, Overholser JC, Butt ZA. Association of substance abuse and depression among adolescent psychiatric inpatients. *Can J Psychiatry* 2003;48(11):762–5.
- [41] Licanin I, Music E, Laslo E, Berg-Kelly K, Masic I, Redzic A, et al. Suicidal thoughts related to psychoactive substance abuse among adolescents. *Med Arh* 2003;57(4):237–40.
- [42] Walkup JT, McAlpine DD, Olfson M, Labay L, Boyer CA, Hansell S. Is the substance abuse of inpatients with schizophrenia overlooked? *Gen Hosp Psychiatry* 2001;23(1):26–30.
- [43] Kanwischer RW, Hundley J. Screening for substance abuse in hospitalized psychiatric patients. *Hosp Community Psychiatry* 1990;41(7):795–7.
- [44] Barnaby B, Drummond C, McCloud A, Burns T, Omu N. Substance misuse in psychiatric inpatients: comparison of a screening questionnaire survey with case notes. *BMJ* 2003;327(7418):783–4.
- [45] Farrell MP, David AS. Do psychiatric registrars take a proper drinking history? *BMJ (Clin Res Ed)* 1988;296(6619):395–6.
- [46] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington (DC): American Psychiatric Press; 1994.
- [47] First MB, Spitzer RL, Gibbon RL, Williams M, Janet BW, Loma B. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II), (Version 2.0)*. New York: Biometric Research Department, New York State Psychiatric Institute; 1996.
- [48] WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD assignment*. 3rd ed. Oslo: WHO; 2000.
- [49] Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep* 1962;10:799–812.
- [50] Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
- [51] Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The overt aggression scale for the objective rating of verbal and physical aggression. *Am J Psychiatry* 1986;143(1):35–9.
- [52] Teichman M, Rahav G. *The annual survey of substance use in Israel*. Jerusalem: The Israeli Anti Drug Agency; 2002.
- [53] Bejerot S, Nylander L. Low prevalence of smoking in patients with autism spectrum disorders. *Psychiatry Res* 2003;119(1-2):177–82.
- [54] Abood ME, Martin BR. Neurobiology of marijuana abuse. *Trends Pharmacol Sci* 1992;13(5):201–6.
- [55] Brady KT, Randall CL. Gender differences in substance use disorders. *Psychiatr Clin North Am* 1999;22(2):241–52.
- [56] Stein MD, Cyr MG. Women and substance abuse. *Med Clin North Am* 1997;81(4):979–98.
- [57] Greenfield SF, Manwani SG, Nargiso JE. Epidemiology of substance use disorders in women. *Obstet Gynecol Clin North Am* 2003;30(3):413–46.
- [58] Hovens JG, Cantwell DP, Kiriakos R. Psychiatric comorbidity in hospitalized adolescent substance abusers. *J Am Acad Child Adolesc Psychiatry* 1994;33(4):476–83.
- [59] Kendler KS. A twin study of individuals with both schizophrenia and alcoholism. *Br J Psychiatry* 1985;147:48–53.
- [60] Sanguinetti VR, Samuel SE. Comorbid substance abuse and recovery from acute psychiatric relapse. *Hosp Community Psychiatry* 1993;44(11):1073–6.
- [61] Sanguinetti VR, Samuel SE, Schwartz SL, Robeson MR. Retrospective study of 2,200 involuntary psychiatric admissions and readmissions. *Am J Psychiatry* 1996;153(3):392–6.
- [62] Selzer JA, Lieberman JA. Schizophrenia and substance abuse. *Psychiatr Clin North Am* 1993;16(2):401–12.