Drug and Alcohol Use among Patients with Schizophrenia and Related Psychoses: Levels, Consequences and Changes in Psychiatric Symptoms and Substance Abuse at Twelve-month follow-up

By

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ABSTRACT

Patients with schizophrenia and related psychoses frequently use, abuse and become dependent on psychoactive substances. A cross-sectional survey was conducted to document substance abuse in 207 successive outpatients with schizophrenia and related psychoses presenting to a psychiatric continuing care facility in a large Canadian city. Nicotine, alcohol and cannabis were the most frequently abused substances. Excluding nicotine, 44.9% met criteria for lifetime and 14.0% for current abuse/dependence. Current dual diagnosis (DD) patients had significantly more positive psychotic and depressive symptoms, higher rates of medication non-compliance, as well as higher rates of tobacco smoking and significantly longer smoking histories compared to single diagnosis (SD) patients. The smoking behavior of the DD population is discussed in terms of enhanced risk for alcohol abuse, as well as effects on antipsychotic blood levels and metabolism.

In the second phase of the study, the starting sample was reassessed at 4 month intervals out to 12-months of follow-up. The follow-up study was designed to test the hypothesis that current-DD patients would fare significantly worse than SD patients. This study found that during the course of standard psychiatric outpatient treatment there was little decrease in substance use or abuse over time among the DD group. However, DD subjects experienced a greater reduction in positive psychotic symptoms compared to SD patients. The follow up study demonstrated that DD patients in treatment for schizophrenia and related psychoses did reasonably well in terms of reduced psychosis; however they continued to use substances of abuse and remained more depressed than SD.

RESUME

Les patients atteints de schizophrénie et de psychoses du même type utilisent fréquemment, abusent, et deviennent dépendants des substances psychoactives. Une étude croisée a été menée afin de documenter l'abus de substances auprès de 207 patients externes atteints de schizophrénie et de psychoses du même type, se présentant dans une institution de soins psychiatriques continus dans une grande ville canadienne. Les substances dont ils abusaient le plus fréquemment étaient la nicotine, l'alcool et le cannabis. En excluant la nicotine, 44.9% des patients répondaient aux critères d'antécédents de dépendance/abus et 14.0% aux dépendance/abus courants. Les patients à diagnostic double courant (DD) avaient significativement plus de symptômes dépressifs et psychotiques positifs, des taux plus élevés de non-observance à la médication et de consommation de tabac, ainsi qu'un passé significativement plus long de consommation de tabac, en comparaison aux patients à diagnostic unique (DU). La consommation de tabac de la population DD est discutée en termes d'augmentation de risque d'abus d'alcool, ainsi que d'influence sur les niveaux sanguins et le métabolisme d'antipsychotiques.

Dans la seconde phase de l'étude, l'échantillon de départ a été réévalué à 4 mois d'intervalle sur 12 mois de suivi. L'étude du suivi consistait à tester l'hypothèse que les patients courants DD se porteraient significativement moins bien que les patients DU. Cette étude démontra qu'au cours du traitement psychiatrique standard des patients externes, il y a eu peu de baisse d'utilisation ou d'abus de substances dans le groupe DD. Cependant, les sujets DD ont éprouvé une baisse plus forte de leurs symptômes psychotiques positifs que les patients DU. L'étude du suivi a démontré une réduction

raisonnable de la psychose chez les patients DD en traitement pour la schizophrénie et les psychoses du même type, bien qu'ils aient continué à utiliser ou abuser de substances et qu'ils soient demeurés plus dépressifs que les patients DU.

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INTRODUCTION

Dual diagnosis (DD), the co-occurrence of a mental and addictive disorder, is a common problem for patients with schizophrenia and related psychotic disorders. Previous studies have estimated the prevalence to range from 6-60% (Fowler et al. 1998). The Epidemiological Catchment Area study found that 27.5% of patients with schizophrenia had a co-morbid substance abuse disorder (Regier et al. 1990), while 44.8% of individuals with non-affective psychosis were classified as DD in the National Comorbidity Survey (Kendler et al. 1996).

Variation in rates of abuse/dependence among psychotic patient stems from differences in sample size, subject selection, diagnostic criteria, and definitions of substance use disorders. Prevalence of current abuse/dependence in psychiatric inpatients ranges from 12-60% (Brady et al. 1991;Cantwell et al. 1999;Havassy and Arns 1998;Drake et al. 1989), and from 48-64% for lifetime abuse/dependence (Brady et al. 1991;Dixon et al. 1991;Drake et al. 1993). Among outpatients, rates of lifetime and current abuse/dependence vary from 6-60% (el Guebaly and Hodgins 1992;Fowler et al. 1998;Gogek 1991).

Nicotine, alcohol, cannabis and cocaine are the most commonly used substances by patients with psychotic disorders. In the United States about one-quarter of the population are smokers (Hymowitz et al. 1997), while more than 70% of patients with schizophrenia are nicotine dependent (Van Dongen 1999;Ziedonis and George 1997). Alcohol is used by approximately 45-60% of current and former psychotic inpatients (Dixon et al. 1991;Drake et al. 1989;Drake et al. 1993;Hambrecht and Hafner 1996).

While cannabis use is common among the DD population in the United States (31-42%) (Dixon et al. 1991), it is less common in France (27%) (Dervaux et al. 2001), England (18.7%) (Duke et al. 2001) and Germany (5-13%) (Hambrecht and Hafner 2000;Soyka et al. 1993). Finally, 15-50% of patients with schizophrenia in the U.S. have reported cocaine abuse (Schneier and Siris 1987;Ziedonis et al. 1992), compared to 1.5% of patients in Australia (Fowler et al. 1998), and 1% in France (Dervaux et al. 2001). In England 8.7% reported lifetime stimulant abuse including cocaine and amphetamines (Duke et al. 2001). Such variance across different social settings underscores the need for local surveys to explore the extent and nature of problems related to DD.

DD patients present additional difficulties from a diagnostic and clinical management perspective than single diagnosis (SD) patients. Increased aggression and violence (Angermeyer 2000;Soyka 2000) and medication noncompliance have been reported among DD patients (Swartz et al. 1998;Kamali et al. 2001;Olfson et al. 2000). In a review, Angermeyer (Angermeyer 2000) found that patients with schizophrenia had a mean odds ratio for violent behaviour of 3.9-8.0 compared to people without mental health problems. However, DD patients were more likely to commit violent offences (mean OR= 7.2-18.8), and were 17 times more liable to commit homicide compared to the general population. A greater proportion of DD patients were convicted of criminal activity compared to SD patients (40.1% vs. 13.7%) (Soyka 2000).

Substance use has been found to exacerbate psychiatric symptoms and especially the positive symptoms of schizophrenia. Schizophrenics who abuse alcohol reported significantly more hallucinations and depressive symptoms than nonalcoholic schizophrenics (Pulver et al. 1989), and heavy alcohol use was significantly correlated

with hostile threats, paranoia, disorganized incoherent speech, depression and suicidal behaviour (Drake et al. 1989). Continuous delusions were more frequently reported among current cannabis using schizophrenics (43%) compared to past users (21%) or non-users (11%) (Negrete et al. 1986). This study also found similar trends for continuous hallucinations (29% current; 18% past; 6% non-users) (Negrete et al. 1986). Similarly, cannabis-abusing schizophrenics were found to have significantly greater hostility and thought disturbance than schizophrenics who did not use cannabis (Caspari 1999). Patients with schizophrenia who abused cocaine were significantly more likely to have current major depression (Brady et al. 1990) and suicidal ideation (Seibyl et al. 1993). Patients with a cocaine abuse history were more prone to be depressed, less socialized and had more impairment on memory tasks (Sevy et al. 1990). Taken together, these studies point to the negative additive effects of comorbid substance use among psychotic patients, leading to exacerbation or continued psychosis, and poorer social functioning.

Some studies have suggested that only a small percentage of patients with severe mental illness (SMI) achieve stable substance use remission, similar to substance abusers without SMI (Drake et al. 1996). The prevalence of active substance use disorders changed little during a 7-year naturalistic follow-up (Bartels et al. 1995) suggesting that remission and new cases were approximately equal. Another report, which found high remission rates among dually diagnosed patients, did not specify the prevalence of each type of mental illness in the sample that remitted (Dixon et al. 1998). Furthermore, this study reported significantly higher dropout rates among patients with schizophrenia and other psychoses compared to patients with other diagnoses (Dixon et al. 1998).

In a retrospective 18-month study of 100 schizophrenic outpatients, between 30-40% were found to be using substances during each 3-month interval (Chouljian et al. 1995). Analysis of 59 of the subjects with complete data demonstrated that usage levels did not change significantly over time. However, in this same subset, problem use of cocaine and multiple substances increased, while problem use of alcohol, marijuana and other drugs remained stable (Chouljian et al. 1995). Coldham and colleagues found that medication non-compliant first episode psychosis subjects had significantly higher levels of alcohol and cannabis use at baseline and 1-year follow up (Coldham et al. 2002).

In the literature to date there are few prospective studies of DD, and the existing prospective studies are either heterogeneous with respect to Axis I diagnosis (for example (el Guebaly et al. 1999;Bogenschutz and Siegfreid 1998;Sloan and Rowe 1998) or suffer from small sample sizes (N<30). Owen et al. (Owen et al. 1996) ascertained that DD outpatients with schizophrenia who were non-compliant with medication and had no outpatient contact over a six month follow-up had significantly higher BPRS scores compared to SD or DD patients who were either compliant, had outpatient contact, or both. However the number of patients meeting criteria for this high-risk group was not reported and was probably small since only 31/135 (23%) subjects had current substance abuse or dependence at follow-up, and only 20/135 (15%) were non-compliant at follow up (Owen et al. 1996). Caspari (Caspari 1999) examined the impact of cannabis abuse on schizophrenia with a follow-up sample of 27 DD patients compared to 26 SD controls. He found higher rehospitalization rates and worse psychosocial functioning in the cannabis abuse group at follow up after 68.7±28.3 months. The cannabis group also had additional thought disturbance measured on the Brief Psychiatric Rating Scale (BPRS)

and hostility measured on the Arbeitsgememeinscaft fur Methodik und Dokumetation in der Psychiatrie (AMDP) (German equivalent scale for measurement of psychotic symptoms) compared to the control group at follow up, but this particular result was cross-sectional, not a repeated measure. Of note, at follow-up Caspari (Caspari 1999) found that 48% of the DD patients had ceased all substance abuse, while only one SD patient started excessive alcohol use, and none showed significant drug use.

It remains possible that increased symptoms in DD are not accounted for by non-compliance alone and that there is a direct effect of substances of abuse on expression of psychiatric symptoms. However, Blow et al. (Blow et al. 1998) found *lower* levels of psychotic symptoms measured on the BPRS among dual diagnosis as compared to single diagnosis patients. They also found that over a 2 year follow up period, DD subjects improved more that SD subjects on clinician rated Global Assessment of Functioning. While DD subjects had a greater number of admissions, the 2 groups did not differ in total inpatient days. Unfortunately, Blow et al. (Blow et al. 1998) did not explore changes in drug use prevalence or severity during the follow up period. Buhler et al. (Buhler et al. 2002) followed 29 DD and 29 SD first episode patients for five years. Among these patients available for follow up assessments, DD subjects had more positive symptoms and less affective flattening (Buhler et al. 2002). Once again, changes in drug use prevalence or severity during the follow up period were not explored.

OBJECTIVES OF THE RESEARCH

Most previous dual diagnosis studies have been conducted in the United States. The present study was conducted in Quebec, Canada. This province is distinct culturally and linguistically and the legal drinking age is 18. (In most North American jurisdictions the legal drinking age is 19 or 21). The study consists of 2 parts. The first part presents data collected at the start of a 12-month longitudinal survey and explores the impact of substance abuse on psychiatric symptoms measured at intake. The first objective was to determine the proportion of patients with schizophrenia and related psychoses meeting the criteria for dual diagnosis, both current and lifetime, within an urban Canadian population. Determination of the types of substances used by Canadian patients with dual diagnosis was another objective as these have been shown to differ by country of origin. In the second part of the study, the objective was to examine the effects of substance use on the outcome of treatment for chronic mental illness, including schizophrenia, schizoaffective disorder and related psychoses. The primary hypothesis to be tested was that mentally ill patients with a lifetime and/or current diagnosis of a substance use disorder would fare significantly worse than non-using patients in terms of a number of measures of outcome.

The objectives of the study were met by conducting a detailed prospective study of the relationship between substance abuse and the ongoing course of illness in a group of psychiatric patients newly admitted to the Continuing Care Service at the McGill University Health Centre. All patients were assessed at intake using a detailed protocol with the use of standardized instruments to confirm the diagnosis of psychiatric illness and substance use disorders (Structured Clinical Interview for DSM-IV or SCID),

measure psychiatric symptoms (Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HAM-D), Brief Symptom Inventory (BSI), Satisfaction with Life Domains Scale (SDLS)), and ascertain current patterns of substance use (Addiction Severity Index (ASI)). Patients were re-interviewed at four month intervals up to one year of follow-up. The use of these standardized instruments for a specific diagnostic group sets this study apart from most other previous reports.

Statistical analyses determined whether there were differences in severity of psychiatric symptomatology and functioning over the year among three groups; those with no substance use (Single Diagnosis, SD), those with current substance abuse/dependence (Dual Diagnosis (DD–current) and those with a lifetime history of substance abuse/dependence (DD-lifetime). Variables included addiction severity (composite scores on the Addiction Severity Index), the number and duration of rehospitalizations, number of visits to the emergency services, antipsychotic dose in chlorpromazine equivalents, quality of life scores, psychiatric symptomatology measured by the Positive and Negative Syndrome Scale (PANSS) (positive, negative and global scales), and Hamilton depression rating scale, and subjective distress (rated by the Brief Symptom Inventory).

METHODS

Research Site and Subjects

The research was conducted in the Continuing Care Service (CCS) at the McGill University Health Centre (MUHC), Montreal General Hospital (MGH) site. The CCS is located in the outpatient psychiatry department of the MGH in central Montreal. The CCS is an outpatient service that serves a population of patients with chronic or recurring psychosis (schizophrenia and related psychoses) from a defined geographical catchment area. The catchment area (defined by home postal code) required patients to obtain all psychiatric services and follow-up at the MGH. The MGH catchment area is wide, representing a multicultural population from both inner city and suburban regions with variation in terms language and socio-economic status. Patients with acute and first episode psychoses were treated at specialized units at another hospital site.

All new patients presenting to the CCS were informed of the study during their initial clinic assessment interview Written informed consent for additional interviews (compensated with $20 in coupons for food, clothing etc), as well as urine toxicology screening and a chart review were requested by the Clinical Research Coordinator. This recruitment procedure resulted in an 80.2 % participation rate overall; 14% refused consent and an additional 5.8% were considered to be unable to give consent and/or unable to participate. Post-hoc analysis failed to demonstrate any significant differences in terms of distribution by gender, age or clinical diagnosis between those that participated vs. those that refused consent. Only patients meeting DSM-IV diagnostic criteria for schizophrenia or related psychoses (schizoaffective, delusional disorder, psychosis NOS) were included in the sample and subsequent analyses presented below.

Patients meeting criteria for substance-induced psychosis or bipolar disorder were excluded.

For the prospective sample baseline measures were compared to data collected at the study endpoint (12-month). While patients were evaluated at 4-month intervals, the complete set of evaluations was performed only at study entry and study completion. Furthermore, some patients available at 12 months were not available at some of the intervening time points, and vice versa. A comparison of baseline to study end point measures was chosen in order to maintain the maximum possible sample size.

Treatment during follow-up period

The CCS provides long-term care with a focus on improving quality of life, encouraging community living, prevention of hospitalizations and increased autonomy. Clients are treated by a multidisciplinary team that includes a psychiatrist, general practitioner, social worker, nurse and occupational therapist. Each client is followed by a case manager who becomes the primary contact person for both the client and family. A number of services are offered throughout treatment including medication and side-effect management, supportive psychotherapy, crisis intervention, social skills training, as well as linkage with community services related to general health care, housing, finances, vocational training and recreation.

Follow-up sample

At twelve- months, 147/207 patients (71.0%) were still receiving services at the CCS and agreed to the follow up interview. Follow-up rates were 66.1% for SD, 73.5%

for DD-lifetime, and 82.1% for DD-current subjects (x^2=3.3, df=2, p=0.190). Compared to those lost to follow-up, subjects remaining in the study were significantly older (mean age 39.6±10.4 vs. 36.2±10.9; p=0.03), were more apt to live alone (37.0% vs. 19.7%; p=0.05) and had significantly lower PANSS negative scores at intake (15.8±5.2 vs. 17.6±5.6; p=0.03). There were no differences between subjects remaining in the study and those lost to follow-up on any other demographic, psychiatric, or drug use variable. All analyses for the prospective study were conducted on the 147 patients in the 12-month follow-up sample.

Instruments used for data collection

The mood, psychotic, and psychoactive substance abuse sections of the Structured Clinical Interview for DSM-IV (SCID-P) (Spitzer et al. 1990) were administered during the initial intake interview. Patients were excluded from the study if the clinical and/or hospital chart diagnosis of schizophrenia or related psychosis was not confirmed by the SCID-P. Based on the SCID interview patients were categorized at intake into the following groups 1) SD - no current or lifetime diagnosis of any substance use disorder 2) DD-current - current diagnosis of any substance use disorder 3) DD-lifetime – with a lifetime diagnosis of any substance use disorder, no current disorder.

Baseline demographics including age, ethnicity, education, marital status, and personal and family psychiatric history were collected. Date of onset of psychiatric symptoms, number and length of previous hospitalizations, and medications prescribed (dose, form) were obtained from the baseline and follow-up patient interviews and review of previous hospital charts. Compliance was determined during the baseline and follow-up interviews, as a series of questions about the patients' medications, which included

how often they took their medications and whether they took more or less than prescribed. They were scored as non-compliant in the database if they skipped doses, never took them, or took them less than prescribed.

Psychiatric symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Depression Rating Scale (HAM-D), while subjective psychological distress was measured with the Brief Symptom Inventory (BSI). The PANSS is a 30-item standardized instrument that measures positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. affective blunting, emotional withdrawal), and general symptoms (e.g. motor retardation, anxiety, disorientation) using a semi-structured interview and chart review (Kay et al. 1988;Kay et al. 1989). This instrument has been shown to have strong psychometric properties and to be useful in detecting changes in symptoms of schizophrenia and related psychotic disorders over time (Bell et al. 1992). The HAM-D is a 23-item clinician administered scale that rates cognitive, affective, somatic, and vegetative symptoms of depression (HAMILTON 1960). The BSI is a 53-item self-rating questionnaire that evaluates psychological distress in nine areas (e.g. hostility, depression, somatization, anxiety) over the past week (Derogatis and Melisaratos 1983). A global severity index (GSI) score is also obtained from the nine dimensions providing an indication of overall distress. Additionally, a positive symptom total (PST) gives a measure of the total amount of positive symptoms the patient reports whereas a positive symptom distress index (PSDI) is a measure of the distress experienced as a result of positive symptoms (Derogatis and Melisaratos 1983).

The Addiction Severity Index (ASI) was used to determine current and lifetime drug and alcohol use levels (McLellan et al. 1980;McLellan et al. 1985). The ASI was

found reliable and valid for assessing drug-related behaviours and consequences in mentally ill patients (Carise et al. 2001;Hodgins and el Guebaly 1992). It assesses the number of days and routes of administration of specific drug (e.g. cannabis, cocaine, amphetamines etc.) and alcohol use during the past 30 days, as well as the number of days of drug abstinence and extent of substance abuse treatment. Tobacco smoking status and caffeine intake status were also assessed with the ASI.

Tardive Dyskinesia (TD) was evaluated using the Abnormal Involuntary Movement Scale (AIMS) (Simpson et al. 1979;Lane et al. 1985). The AIMS is a 10-item scale assessing individual body movements as well as overall severity of TD.

For the prospective follow-up sample, quality of life (QOL) was measured by the Satisfaction with Life Domains Scale (SDLS). The SDLS is a seven-point scale wherein stylized faces are used to rate patients' feelings about relationships, autonomy, leisure activities, health, housing and economic status (Baker and Intagliata 1982). It has been widely used with mentally ill patients (Baker and Intagliata 1982;Mercier et al. 1992) and it has been demonstrated to have good psychometric properties in terms of reliability, internal consistency, and convergent and content validity (Kamman et al. 1983;Horley 1985;Larsen et al. 1985).

Statistical Analysis

Data for each patient across all variables including demographic and diagnostic information, PANSS, HAM-D, ASI, BSI, AIMS, and SDLS was coded and entered into a database using Microsoft Excel®. Statistical analysis was conducted using the microcomputer version 10.0 of SPSS® (SPSS Inc. 2000). Fisher's exact tests and chi-

square tests of association were used to assess differences in categorical variables between three groups 1) patient with a current substance use disorder diagnosis (current-DD) 2) patients with a lifetime substance use disorder diagnosis (lifetime-DD) and 3) patients with no current or lifetime substance use disorder diagnosis (SD). Categorical variables included demographics, prescribed medications, compliance status, and substances of abuse used by each group of patients within the past 30 days. Comparisons between groups for continuous variables were conducted using independent t-tests and Analysis of Variance (ANOVA) techniques, including multivariate tests (MANOVA). Post-hoc tests were performed using t-tests with a Bonferroni correction. Continuous variables included age and age related variables (e.g. age first received help), severity of psychiatric symptoms on the PANSS, HAM-D, BSI, years of substance use across both substance types and patient groups.

The follow up study was designed to test the hypothesis that DD patients with a current diagnosis of substance abuse/dependence would fare significantly worse than non-using SD patients over a number of measures of outcome. Power analyses were conducted in order to determine whether the follow-up sample was adequate to test the primary hypothesis. There are no standard methods for power/sample size calculations in the context of multivariate models for unbalanced repeated measures MANOVA. Approximate power was determined by generalizing conventional multiple linear analysis to the case of repeated measurements of an interval-scale dependent variable. Calculations indicated that a total sample of 140 patients would be required to ensure 80% power in a 2-tailed test ($p = 0.05$) of the significance of the difference between current drug abusers and other patients, after having adjusted for potential confounders (e.g. age, gender).

RESULTS

Characteristics of the baseline sample

Demographic characteristics of DD and SD populations are shown in **Table 1**. The cohort was a chronically ill population with approximately 16 years since first diagnosis. The sample was comprised of patients with a primary diagnosis of schizophrenia (n=128), schizoaffective disorder (n=52) and related psychotic disorders (psychosis NOS, delusional disorder) (n=27). Of the 207 patients in the sample, 93 (44.9%) were classified as DD and 114 (55.1%) as SD. Among the 93 DD patients, 29 (31.2% and 14.0% of the entire sample) met DSM-IV criteria for current substance use disorder, while the remaining 64 (68.8%) had a lifetime diagnosis. Other than gender composition and age at first psychiatric treatment, DD and SD patients did not differ significantly on any other socio/demographic variable. Demographic data also did not differ between current DD and lifetime DD groups.

Medications prescribed were similar for the two groups (**Table 2**). However, DD patients had a significantly higher rate of self-reported medication non-compliance than SD patients (19.1% versus 4.5%) with an even higher rate among current DD at 27.6%.

Substance use, abuse and dependence at baseline

In this sample, 65.2% had smoked cigarettes, 47.3% used alcohol, while 20.0% used at least one drug of abuse excluding alcohol, within the previous 30 days. Cannabis was the most commonly used drug (12.1%), followed by benzodiazepines (7.8%; defined as using more benzodiazepines than prescribed) while only 3.9% used cocaine. Other substances were infrequently reported as shown in **Table 3**. As noted above 14.0% met

DSM-IV criteria for current (past month) substance use disorder excluding nicotine and caffeine. Alcohol (10.1%) and cannabis (8.2%) were the most commonly abused substances, followed by cocaine (2.9%) benzodiazepines (1.5%) and opiates (1.0%).

Rates of current alcohol and drug use by diagnostic sub-group are shown in **Table 4**. Not surprisingly, a significantly greater proportion of current DD subjects used both alcohol and drugs. It was notable that smoking was much more pervasive among both current (88.4%) and lifetime (84.1%) DD subjects; while 49.6% of SD patient smoked at least one cigarette in the previous 30 days. Current DD patients used alcohol, drank to intoxication, and used cannabis significantly more often in the previous 30 days than both SD and lifetime DD subjects.

Over the month prior to assessment, current-DD patients spent significantly more money on both alcohol (DD= $58.54±$124.60 vs. SD= $3.28±$12.0, $p<.001$) and drugs (DD= $53.17±$73.72 vs. SD= $0.26±$2.08, $p<.001$) compared to the SD group. These amounts are considerable given that 71.0% of the DD patients were on social welfare, which provides them with $537 - $776 per month for all expenses.

Lifetime-DD and current-DD patients had longer histories of drinking to intoxication and cannabis use compared to SD (**Table 5**). History of cocaine and cigarette use was significantly longer for current-DD compared to SD patients.

Psychiatric symptomatology at baseline

Current-DD patients had significantly higher PANSS positive psychotic scores than both lifetime-DD and SD patients (**Table 6**). While there were no significant group differences on the mean total HAM-D scores, a greater proportion of patients with

current-DD had HAM-D scores in the depressed range of 12 or more (69.0%) compared to DD-lifetime (46.9%) and SD patients (45.6%). Patients with current-DD reported more symptoms on the BSI in terms of the GSI compared to SD subjects, and the PST compared to both SD and DD-lifetime patients. There were no between group differences on either the total or individual items of the AIMS or in expression of symptoms related to prescribed antipsychotic type (data not shown).

Characteristics of subjects at study end point

Subjects with dual diagnosis (DD –current or lifetime) were more likely than single diagnosis (SD) to be male and non-compliant with medications at intake and younger when they first received psychiatric treatment (**Table 7**). There were no significant differences between SD and DD patients on any other demographic variable. Of note, at follow up medication compliance rates were similar among the 3 groups, with DD subjects showing an increase in medication compliance over the follow-up period. Because of the naturalistic study design, and use of concomitant medications including antidepressants, anticonvulsants, and benzodiazepines which can all influence antipsychotic levels, changes in antipsychotic dose and type were not analyzed as this created too many small subgroups which did not lend themselves to any meaningful analysis.

Only 15% (22/147) of patients required hospitalization during the follow up period and most needed either 1 (N=14) or 2 (N=6) hospitalizations. There were no significant differences between groups (SD, DD-current, DD-Lifetime) with respect to hospitalizations.

Substance use, abuse and dependence at study end-point

Primary substance of abuse for DD current and DD lifetime patients is shown in **table 8**. A higher percentage of current DD subjects used cannabis while a lower percent used both alcohol and cocaine compared to DD lifetime subjects. These differences were not statistically significant.

The levels of substance use as measured by the addiction severity index did not differ significantly when comparing baseline to 12-month follow-up measures. There were no significant time [$F(1,135)=1.42$, $p=.24$] or group x time interactions [$F(2,135)=0.34$, $p=.72$]. This lack of change was seen not only for overall substance use, but also when examining alcohol (all p values >0.3) (**Figure 1**) and drug (all p values >0.2) (**Figure 2**) use measures separately.

Psychiatric symptomatology at study end point

During the course of standard psychiatric outpatient treatment at the CCS, DD subjects experienced a greater reduction in PANSS positive symptom measures compared to SD patients at 12 months (**Table 9, Figure 3**). Repeated measures ANOVA with group (3 levels) and time (2 levels) factors yielded significant effect of time [$F(1,140)=47.50$, $p=.0001$] and a significant group x time interaction [$F(2,140)=3.97$, $p=.021$]. The DD-current group showed the largest drop in PANSS scores (-28% change from baseline) over the follow-up period. Post-hoc analysis failed to reveal a statistically significant between group difference at time 2 (12 months). Thus, at 12 months all groups tended to look similar in terms of positive symptom expression.

HAM-D total scores were analyzed using repeated measures ANOVA with group (3 levels) and time (2 levels) factors yielding a significant main effect for group [$F(2,138)=5.41$, $p=.005$] and time [$F(1,138)=4.92$, $p=.028$] but no group x time interaction [$F(2,138)=0.379$, $p=.685$]. Post-hoc analysis with Bonferroni correction demonstrated a significant difference between SD and DD current groups ($p=.008$) at 12 months (time 2). Thus, over the follow-up period all groups showed a reduction in mean HAM-D total scores but DD-current subjects had the smallest mean reduction. Substance abuse did impact on rates of clinically significant depression as 62.5% of current DD and 50% of lifetime DD versus only 34.7% of SD patients had HAM-D scores in the depressed range of 12 or more at follow-up ($X^2=0.039$, $df=2$).

Additional variables related to psychological status at baseline and 12 month follow-up (PANSS, BSI, SDLS) are presented in **Table 9.** While there was a trend for differences between the SD versus DD-current and DD-lifetime subjects on total subjective QOL scores, these were not significant when corrected for multiple comparisons.

Subjective symptom measurements were different between SD, DD-lifetime and DD-current groups as measured by the BSI. While all groups showed some reduction in their level of distress as measured by the Global Severity Index (GSI), scores remained the most elevated for current DD subjects [$F(2,139)=9.39$, $p<0.001$] (**Figure 4**). Furthermore, while all three groups had some reduction in their Positive Symptom Total (PST) scores, the DD-current group remained the most symptomatic, followed by the DD-lifetime group [$F(2,142)=10.30$ $p<0.001$] (**Figure 5**). These results remained significant after correction for multiple comparisons.

DISCUSSION

Baseline study

In the present study at baseline, 44.9% received a DSM-IV diagnosis of lifetime substance use disorder. This is comparable to previously reported outpatient samples in the United States, Australia and Europe. Rates of current substance abuse/dependence (14.0%) were lower than previous comparable studies. This is most likely related to use of DSM-IV diagnostic criteria, as well as the fact that current was defined as abuse within the previous 30 days. In the Fowler et al. (Fowler et al. 1998) study, comparable to the present study in terms of sample size and methods, current use was classified within a 6-month time frame. In their sample 26.8% (n=194) had a current substance-use disorder. However, defining "current" over a 6-month time frame may be too long as subjects who have achieved 5 months of abstinence are grouped with those who used the day prior to the survey.

Not surprisingly, the most commonly abused substances at baseline were nicotine, alcohol and cannabis. Cigarette smoking was relatively frequent among subjects in the sample with 65.2% reporting some use and 58.4% reporting daily use in the past month. However, the level of smoking in the present sample appears lower than other studies where 70-90% were found to be nicotine dependent (Van Dongen 1999;Ziedonis and George 1997). The finding that only 49.6% of SD patients had used nicotine in the past month is indeed important and may reflect the fact that non-smoking patients with schizophrenia are possibly more health conscious (Ziedonis and George 1997). Nicotine's ability to temporarily normalize auditory evoked potential deficits in some but not all schizophrenics, possibly via the alpha7 subunit of the nicotinic acetylcholine

receptor has also been suggested as a reason for the high rate of nicotine dependence among some patients with schizophrenia (Adler et al. 1998). Importantly, current-DD subjects had significantly longer histories of smoking cigarettes than SD patients (19.1 ± 11.2 versus 11.5 ± 14.2 years), suggesting that early cigarette use may serve as a risk factor or marker of future involvement with other substances of abuse among patients with schizophrenia. Among non-psychotic individuals with substance use disorders, nicotine use is closely associated with alcohol intake. For example, the occurrence of alcoholism is substantially increased in smokers compared to non-smokers and up to 95% of alcoholics are concurrent smokers (DiFranza and Guerrera 1990). In addition, research suggests that early tobacco use may be associated with increased vulnerability for subsequent alcohol use (Abelson et al. 2002;Hughes 1995). A study of 3356 male twin pairs found a substantial genetic correlation (r=0.68) between nicotine and alcohol dependence (True et al. 1999), suggesting that overlapping genetic factors contribute to the clinical and epidemiological associations. Common genetic vulnerability is only one possible mechanism however, and the association between alcohol and nicotine may also be due to shared risk factors (i.e. self-medication of psychological distress), which may be especially prevalent in the DD population.

Smoking can alter medication blood levels making pharmacological interventions quite complex. Certain agents in tobacco smoke increase the metabolism of antipsychotic medications through induction of hepatic cytochrome (CYP) P450 enzymes and especially CYP450 1A2 (Nemeroff et al. 1996;van der Weide and Steijns 1999). For example, in one study with 11 patients, clozapine levels increased by a mean 57.4% upon smoking cessation because CYP450 1A2 is the major metabolic pathway for clozapine

metabolism (Meyer 2001). Additionally, olanzapine clearance is 37-48% lower in non-smokers as compared to smokers (Callaghan et al. 1999). Once again, this is because olanzapine is largely metabolized through CYP450 1A2 (Callaghan et al. 1999). Patients with DD who smoke at a higher rate than SD patients may eliminate their medications faster, and subsequently experience a higher rate of psychiatric impairment. In this study the DD groups smoked on a greater number of days (DD current 26.7±9.6; DD lifetime 24.1±14.5) than the SD group (12.4±14.7) over the past month. Although plasma levels of antipsychotics were not measured, the higher rate of smoking may have contributed to increased impairment in the DD groups.

At baseline, alcohol was used by 47.3% of the cohort, while 10.1% had a history of alcohol abuse/dependence. Cannabis was used by 13.1%, and abuse/dependence by 8.2% of this cohort. These rates are lower than previous similar studies where 12.3-50% had histories of alcohol abuse/dependence (Alterman et al. 1981;Drake et al. 1990) and 12.5-35.8% had cannabis abuse/dependence histories (Barbee et al. 1989;Cohen and Klein 1970;Fowler et al. 1998). Cocaine was used by 3.9% of the sample, but only 2.4% had current abuse/dependence. This finding is more similar to the experiences in Australia where 1.5% reported cocaine use in the previous 6 months (Fowler et al. 1998), and France where 1% reported lifetime cocaine abuse (Dervaux et al. 2001), as compared to the US where 10-15% of patients abuse cocaine (Dixon et al. 1991).

In the present cohort at study entry, positive psychotic symptoms were greatest for the current-DD group. This suggests that substance abuse affects positive but not negative symptoms of schizophrenia. It is possible that the increased psychopathology can be accounted for by increased medication noncompliance among current-DD subjects

(27.6%), versus 15.0% among lifetime-DD and 4.5% among SD patients. This finding validates previous literature examining non-compliance in psychotic patients with DD (Fenton et al. 1997;Heyscue et al. 1998;Swartz et al. 1998;Bhanji et al. 2004). For example, Kamali et al. (Kamali et al. 2001) used logistic regression analysis to find that current comorbid substance misuse and poorer insight into illness were significantly associated with poor antipsychotic compliance among patients (n=66) with schizophrenia or schizoaffective disorder. In a larger sample (n=213) of patients with schizophrenia or schizoaffective disorder, substance use (OR=4.6, CI=1.7-12.0), history of noncompliance (OR=4.1, CI=1.3-12.2), and family refusal to participate in treatment (OR=3.4, CI=1.1-10.3), significantly predicted medication noncompliance in the first three months after hospital discharge (Olfson et al. 2000).

All antipsychotic medications are dopamine receptor (D_2) blockers while drugs of abuse are direct or indirect dopamine agonists. Breen and Thornhill (Breen and Thornhill 1998) suggest that DD patients become non-compliant through 2 mechanisms 1) antipsychotic blockade of dopamine mediated euphoria from the drug of abuse and 2) lack of efficacy of antipsychotic due to ongoing substance use with consequent loss of faith in the treatment. Other reasons for non-compliance among schizophrenic patients in general include cognitive problems, which typically lead to both working and long-term memory difficulties, which often result in forgotten doses (Donohoe et al. 2001). In addition, cognitive problems result in practical issues such as difficulties budgeting money for medication, obtaining or storing medication refills, etc. (Bhanji et al. 2004). A study examining predictors of medication discontinuation by patients with first-episode schizophrenia found that patients with poorer premorbid cognitive functioning were more

likely to stop medication (Kampman et al. 2002). Therefore the greater the degree of cognitive deficits, the greater the likelihood of compliance problems. However, DD first-episode patients were found not to have increased cognitive impairment as compared to SD first-episode patients (Pencer and Addington 2003). A poor awareness of illness may also lead to non-compliance (Pyne et al. 2001). Adverse effects from the primary pharmacotherapy or deliberate underdosing by patients (covert partial noncompliance), can result in additional medications prescribed to deal with consequences, with resulting pitfalls (Kane and Nemec 2002). Fear of developing adverse effects from pharmacotherapy is another reason patients choose to not comply with treatments (Bhanji et al. 2004). Finally, some reports found that the development of dose-related extrapyramidal symptoms such as akinesia, akathisia, or Parkinsonism is a frequent reason cited for noncompliance (Misdrahi et al. 2002;Kane and Nemec 2002). In the present study, lifetime-DD and SD patients had equivalent levels of positive psychopathology despite unequal rates of non-compliance, arguing for a direct role of current substance use, for example cigarette smoking as detailed above, in increasing positive symptoms of schizophrenia.

Clinically significant depression as measured by the HAM-D was more frequent among current-DD patients compared to the other two groups at baseline. This may be related to self-medication, as depressed persons may be more prone to use licit and illicit substances to alleviate depressed mood, and/or to a direct depressant effect of the substances of abuse.

Limitations of the baseline study include the cross sectional design in which psychiatric symptoms were measured at one point in time. Since psychiatric symptoms

vary and are expected to vary with the patterns of current substance use, the relationship between use and expression of psychiatric symptoms could not be explored in this study. As well clinical samples are by their nature biased. However, this was a sample from a large catchment area and the refusal rate of the sample (14%) was relatively low. Furthermore, this study relied on self-report data, which underestimates medication non-adherence as well as current substance abuse; thus some SD patients may have been incorrectly classified as SD instead of DD.

Prospective follow-up study

Of the initial cohort, 71% were followed for 12-months, a reasonably good follow-up rate for this chronic psychotic population. While the numbers did not reach statistical significance, there was a trend for current (82.1%) and lifetime DD (73.5%) groups to have a higher rate of maintaining outpatient treatment at the CCS compared to the SD group (66.1%). This is contrary to Bootsmiller et al. (BootsMiller et al. 1998) who reported that dual diagnosis subjects have a high attrition rate and are difficult to track in follow-up studies. However, it is consistent with reports that demonstrate that DD patients require additional treatment services and incur higher costs that SD patients (Maynard and Cox 1998;Woogh 1990).

The follow up study demonstrates that when DD patients with schizophrenia and related psychoses are treated for their psychiatric illness they do reasonably well in that psychosis is reduced. Moreover, the reduction in psychosis is not related to the type of antipsychotic prescribed (typical vs. atypical). With routine outpatient treatment they in fact tend to have similar positive psychotic symptomatology to SD patients despite the

fact that they continue to use substances of abuse. While somewhat counterintuitive, these data suggest that with psychiatric treatment, even one that does not specifically address their substance use, DD patients do no worse than SD patients with respect to psychiatric symtomatology, living arrangements, employment status, etc. However, Canadian patients may be at an advantage as compared to those living in the United States, due to more widely available and Health Care, along with welfare (social assistance), which is not universally available in the United States. Moreover, the lower rates of cocaine use disorders in the present study may also help to explain some of these differences.

In this study, it is not possible to comment on those most difficult DD patients, the revolving door, in and out of inpatient and ER, non-compliant patients. These patients may have been among those lost to follow-up in this sample. However, it is important to remember that statistically, these patients represent a small proportion of DD subjects. Nonetheless, they are often a focus of administrators do to their high resource utilization. It is perhaps only for these patients that targeted, specific programs that address both their psychotic and substance use disorders at the same time is warranted. This population remains an even greater challenge as co-morbid diagnoses, especially personality disorders, are frequently observed.

The results presented here differ than the most comparable published trial to date. Blow and colleagues explored inpatient use and functioning over 2 years in 632 serious mentally ill veterans with an Axis 1 psychotic disorder in whom 90% had schizophrenia, 7.7% an affective psychosis and 198 (29%) had a co-morbid substance use disorder (Blow et al. 1998). Their sample characteristics differ from the present study as they were

all veterans and 96.8% were male. They found that Brief Psychiatric Rating Scale (BPRS) (Overall and Gorman 1962) scores were consistently lower (i.e. better) among DD compared to SD subjects. Clinical rated Global Assessment of Functioning (GAF) scores were higher (better) for DD compared to SD groups and all mean group GAF scores increased between baseline and follow-up. Similar to the findings of this study, DD patients reported less satisfaction with life compared to SD patients on a subjective measure of life satisfaction (Blow et al. 1998). However, unlike the present study, the study by Blow et al. did not evaluate changes in substance use measures over time nor specify the types of substances that were abused.

The baseline, cross-sectional part of this study demonstrated a significantly longer duration of cigarette smoking among current-DD compared to SD subjects. Early cigarette consumption may increase vulnerability to use other substance of abuse including alcohol and cannabis. The tendency for early cigarette use among patients predisposed to develop schizophrenia increases the likelihood that these same individuals will abuse alcohol and other substances, including cannabis.

SUMMARY

In conclusion, for the baseline cohort, patients with schizophrenia and schizoaffective disorder from an urban Canadian center reported lower rates of substance use and, abuse/dependence compared to studies conducted in the United States. It is not clear why this would be the case but more comprehensive social welfare and medical care coverage may in part explain these findings. In this study, current nicotine use was related to use of other substances of abuse, so its use may reflect a more general predisposition to drug dependence among schizophrenics. Finally, current-DD patients have significantly elevated rates of medication non-compliance, positive psychotic symptoms, clinically significant depression, and cigarette smoking compared to SD patients.

In this Canadian cohort, twelve months of outpatient treatment for schizophrenia and related psychotic disorders did not significantly impact levels of alcohol and drug use. All groups experienced a reduction in objective positive symptoms of psychosis. In fact, objective positive symptoms decreased more for DD-current than DD-lifetime than SD patients. This may be related to the fact that those patients who remained in treatment wanted help and so made an effort to be compliant with treatment as compared to those that were lost to follow-up who may have continued to escalate their drug use and /or were more likely to be noncompliant Schizophrenics who abused substances and had higher baseline depression scores which largely disappeared at follow up.

This study suggests that specific efforts to target the majority of DD patients may not be necessary to reduce psychiatric symptoms. However, it is not possible to comment on whether these efforts can improve objective quality of life measures such as

employment status or living arrangements as changes in these variables were not measured in this cohort. Nonetheless, it appears that specific efforts that target those DD patients that are least expected to engage in treatment would best serve to impact on reducing health care costs associated with the DD population.

Table 1: Demographics: Single (SD) versus Dual Diagnosis (DD) at Baseline (n=207)

	SD (n=114)	DD (n=93)
Age (mean years ± S.D.)	39.7±10.5	37.6±10.0
Diagnosis: % Schizophrenia	64.0	59.1
% Schizoaffective disorder	22.8	28.0
% Related Psychotic disorders (psychosis NOS, Delusional disorder)	13.2	12.9
% over age 35	59.6	54.8
% male	46.5	72.0 *
Education: above high school (%)	65.8	55.9
% married	10.5	10.8
% employed	5.3	4.3
% on Welfare (Income from social assistance)	61.4	71.0
% with any DSM-IV mood disorder diagnosis	23.7	29.0
Age first received help (mean years ± S.D.)	24.7±8.2	21.2±8.3 *
Age first hospitalized (mean years ± S.D.)	28.5±9.0 (n=104)	26.4±8.2 (n=82)
Lifetime # of hospitalizations (mean ± S.D.)	4.5±4.6	4.6±5.1
Hospitalizations in last 2 years (mean ± S.D.)	1.2±1.4	1.2±1.6
% with history of medical problems	57.0	56.5
History of current medical problems (%)	40.4	25.0
Living arrangements		
% alone	28.9	35.5
% institution[a]	27.2	25.8
% with others	43.9	38.7

* DD group significantly different than SD group, X^2 or Fisher's exact test, $p<.05$ corrected for multiple comparisons

S.D. = standard deviation

a. Institution includes any supervised living setting

Table 2: Prescribed medications and compliance status at baseline

	SD (n=114)	DD (n=93)
Antipsychotics		
Typical Only (%)	43.0	46.2
Atypical Only (%)	41.2	33.3
Both (%)	11.4	14.0
None (%)	4.4	6.5
% depot antipsychotics	18.4	21.5
Any anti-mania medication (%)	21.9	28.0
Any antidepressant (%)	17.5	23.7
Any benzodiazepine (%)	43.9	40.9
Any EPS medication (%)	35.1	43.0
Non-compliant with medications (%)	4.5	19.1 *

*DD group significantly different than SD group, $p<.05$ corrected for multiple comparisons

SD = Single diagnosis, DD= Dual diagnosis, EPS = Extrapyramidal symptom

Table 3: Current use of substances (past month) at baseline among the entire sample (n=207)

Substance	No Use	Some Use		DSM-IV diagnosis of Abuse/dependence	
	%	%	Days used past month	%	Days used past month
Alcohol	52.7	37.2	3.5±3.9	10.1	7.3±7.2
Cannabis	87.9	3.9	2.8±2.4	8.2	14.7±11.4
Cocaine	96.1	1.0	1.5±0.7	2.9	4.2±4.0
Benzodiazepines	92.2	6.3	5.8±8.1	1.5	2.7±2.1
Amphetamines	99.5	0.0	---	0.5	30±0.0
Hallucinogens	99.5	0.5	1.0 ±0.0	0.0	---
Prescribed narcotics	98.5	0.5	3.0±0.0	1.0	14.0±8.5
Inhalants	99.5	0.0	---	0.5	25.0±0.0
Heroin	99.5	0.0	---	0.5	2.0±0.0
Barbiturates	99.5	0.0	---	0.5	10.0±0.0
Nicotine[a]	34.8	6.8	8.2±8.0	58.4	30.0±0.0
Caffeine[a]	8.7	22.2	10.5±7.8	69.1	30.0±0.0

Values are expressed as the % of subjects using each substance and the mean ± SD number of days used in the past month among those subjects who used substances.
a. For nicotine and caffeine dependence was defined as daily use.

Table 4: Current use of substances (past month) by diagnostic sub-group at baseline

Substance	SD (n=114)	DD-Current (n=29)	DD-Lifetime (n=64)
Alcohol: % using	36.8	89.3*	46.0
Days Used (mean ± S.D.)	1.0±2.13	7.44±7.72*†	1.53±2.33
Days Intoxicated (mean ± S.D.)	0.2±0.9	5.44±8.18*†	0.43±1.12
Cannabis: % using	0	66.7*	11.1
Days Used (mean ± S.D.)	0	9.3±11.42*†	0.33±1.23
Cocaine: % using	0	18.5*	4.8
Days Used (mean ± S.D.)	0	0.56±1.94*	0.21±1.15
Nicotine: % using	49.6	88.9*	84.1*
Days Used (mean ± S.D.)	12.36±14.67	26.67±9.61*	24.13±14.49*
Caffeine: % using	90.2	96.3	90.5
Days Used (mean ± S.D.)	21.88±11.86	27.41±7.41	23.43±11.57

* DD-Current or DD-Lifetime groups significantly different than SD group, $p<.05$
† DD-current significantly different from DD-lifetime group, $p<.05$.
Corrected for multiple comparisons.

SD = Single diagnosis, DD = Dual diagnosis, S.D. = standard deviation

Table 5: Lifetime drug use by diagnostic sub-group

Years of substance use (mean ± S.D.)	SD (n = 104)	DD-Current (n=25)	DD-Lifetime (n=53)
Alcohol	15.95 ± 13.92	20.32 ± 9.64	16.88 ± 12.53
Alcohol Intoxication[a]	1.41 ± 3.79	11.44±11.58*†	5.36 ± 6.71*
Benzodiazepine abuse[b]	0.29 ± 2.94	1.56 ± 4.36	0.15 ± 0.63
Cocaine	0.27 ± 2.12	2.32 ± 3.48*	1.26 ± 3.62
Cannabis	0.26 ± 1.01	8.40 ± 8.39*	5.78 ± 7.27*
Cigarettes	11.51 ± 14.16	19.12 ± 11.19*	16.40 ± 11.06
Caffeine	21.04 ± 13.88	22.84 ± 12.89	17.19 ± 14.19

* DD-Current or DD-Lifetime group significantly different from SD group, $p<.05$.
† DD-Current significantly different from DD-Lifetime group, $p<.05$.
Corrected for multiple comparisons.

SD = Single diagnosis, DD = Dual diagnosis, S.D.= standard deviation
a. Alcohol Intoxication= Based on ASI, mean years of regularly drinking alcohol to intoxication. b. Benzodiazepine abuse= Illicit use or any use above prescribed levels.

Table 6: Psychiatric Symptomatology at baseline: Mean scores on the Positive and Negative Symptom Scale (PANSS), Hamilton Depression Rating Scale (HAM-D), and Brief Symptom Inventory (BSI)

	SD (n=114)	DD-Current (n=29)	DD-Lifetime (n=64)
PANSS (mean ±S.D.)			
Positive	14.25 ± 5.09	18.07 ± 5.18*†	14.70 ± 5.44
Negative	16.71 ± 5.69	15.93 ± 4.96	16.13 ± 5.19
General	30.13 ± 6.56	33.59 ± 7.42	31.16 ± 8.60
Total	61.10 ± 13.77	67.59 ± 13.54	61.98 ± 15.32
HAM-D (mean ± S.D.)			
Mood	3.5 ± 2.7	5.0 ± 2.8	3.9 ± 2.9
Cognitive	1.7 ±2.2	2.2 ± 2.7	2.3 ± 2.8
Vegetative	5.1 ± 3.3	6.4 ± 3.3	5.5 ± 3.6
Mania	4.1 ± 2.8	5.6 ± 3.1	4.7 ± 3.2
Total	12.0 ± 7.2	15.1 ± 7.4	13.4 ± 9.0
BSI (mean ± S.D.)			
GST	0.8 ± 0.7	1.3 ± 0.8*	0.9 ± 0.8
PST	23.8 ± 13.0	33.4± 13.0*†	25.6 ± 13.7
PSDI	1.7 ± 0.7	1.9 ± 0.7	1.8 ± 0.7

* DD-Current or DD-Lifetime group significantly different from SD group, $p<.05$.
† DD-current group significantly different from DD-lifetime group, $p<.05$.
Corrected for multiple comparisons.

PANSS=Positive and Negative Syndrome Scale; HAM-D=Hamilton Depression Rating Scale; BSI= Brief Symptom Inventory, GST=global symptom total, PST=positive symptom total, PSDI=positive symptom distress index

Table 7: Demographics of the sample at follow-up (n=147)

Variable	SD (n=73)	DD-lifetime (n=50)	DD-current (n=24)
Age (mean ± S.D.)	40.4 ± 10.4	40.1 ± 9.7	38.6 ± 10.8
% male	47.9	74.0*	79.2*
Diagnosis at intake			
% Schizophrenia:	63.0	66.0	58.3
% Schizoaffective:	26.0	24.0	16.7
% other (delusional disorder, Psychosis NOS)	11.0	10.0	25.0
% married	9.6	12.0	12.5
% Caucasian	89.0	90.0	95.8
Living arrangements			
% alone	32.9	42.9	37.5
% institution[a]	24.7	22.0	25.0
% with other people	49.7	36.0	37.5
Education: % above high school	65.8	52.0	58.3
% employed	5.5	2.0	0
% on welfare	65.8	68.0	70.8
Age first received help (mean ± S.D.)	24.2 ± 7.9	21.2 ± 9.4	22.0 ± 9.2
Age first hospitalized[b] (mean ± S.D.)	28.2 ± 9.0	25.6 ± 8.6	29.4 ± 9.4
Number of hospitalizations at baseline (mean ± S.D.)	4.6 ± 4.4	4.8 ± 5.4	3.9 ± 3.0
% with history of medical problems	54.8	52.0	58.3
% with current medical problems	42.5	28.0	37.5
% non-compliant at baseline	5.6	20.8*	25.0*
% non-compliant at follow up	10.9	12.0	12.5

a. Institution includes any supervised living setting. b. For age first hospitalized, n=67 for SD, n=45 for DD-lifetime, and n=20 for DD-current as some patients were never hospitalized.

Table 8: Primary Substance of Abuse for Current and Lifetime DD Patients at Study End-Point

Substance of Abuse	DD-Lifetime (n=50)	DD-Current (n=24)	Total sample (n=74)
Alcohol (%)	29.2	40.0	36.5
Cannabis (%)	38.5	32.0	35.1
Cocaine (%)	12.5	20.0	17.6
Other (%)	16.7	8.0	10.8

Table 9: Psychiatric and Substance use measures at baseline and follow-up

Variable	SD (n=73)		DD-Lifetime (n=50)		DD-Current (n=24)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
PANSS						
Positive	14.01±5.36	12.16±5.45	15.22±5.16	12.72±5.16	18.17±5.44	13.04±5.43
Negative	16.10±5.26	14.92±6.63	15.22±5.05	15.11±5.92	15.29±4.93	15.63±5.26
Total	59.90±13.82	54.52±17.52	61.70±13.15	55.96±15.66	66.83±13.53	59.54±16.74
HAM-D Total score	11.7±6.90	9.5±7.7	14.4±8.4	11.7±8.0	15.4±7.5	14.7±7.1
ASI						
Alcohol Composite score	0.02±0.06	0.04±0.08	0.06±0.08	0.09±0.15	0.20±0.20	0.19±0.20
Drug Composite Score	0.006±0.02	0.003±0.008	0.02±0.05	0.02±0.07	0.11±0.11	0.13±0.13
Alcohol and Drug Score	0.03±0.06	0.04±0.09	0.08±0.10	0.12±0.18	0.31±0.23*†	0.32±0.25*†
SDLS						
Total	91.9±18.5	98.6±20.7	88.1±17.7	89.7±20.3	85.3±19.6	86.6±22.3
Daily Activities	29.0±6.2	30.4±7.1	27.9±5.6	28.3±7.0	27.7±5.9	28.4±6.5
Housing	14.6±3.2	14.9±3.8	15.1±3.9	15.0±3.8	14.0±3.4	14.2±3.1
Relationships	12.9±4.3	13.7±4.2	12.2±4.2	12.4±4.2	10.7±5.5	11.6±5.0
Autonomy	26.6±6.4	28.9±6.9	24.6±6.6	25.9±6.8	25.0±6.3	24.9±7.5
Leisure	8.9±2.8	9.5±2.7	8.3±2.7	8.1±3.0	7.8±3.3	7.6±3.1
BSI						
GST	0.80±0.57	0.55±0.55	1.05±0.64	0.84±0.56	1.30±0.72	1.05±0.56
PST	22.7±12.4	17.4±13.5	27.8±12.8	25.6±14.4	33.2±12.6	29.7±14.7
PSDI	1.72±0.68	1.45±0.54	1.88±0.55	1.53±0.43	2.06±0.60	1.74±0.44

PANSS=Positive and Negative Syndrome Scale; HAM-D=Hamilton Depression Rating Scale; ASI=Addiction Severity Index; SDLS=Satisfaction with Life Domains Scale; BSI= Brief Symptom Inventory, GST=global symptom total, PST=positive symptom total, PSDI=positive symptom distress index * DD-Current or DD-Lifetime group significantly different from SD group, $p<.05$. † DD-current group significantly different from DD-lifetime group, $p<.05$. Corrected for multiple comparisons

Figure 1: Change in Addiction Severity Index Alcohol Composite Scores

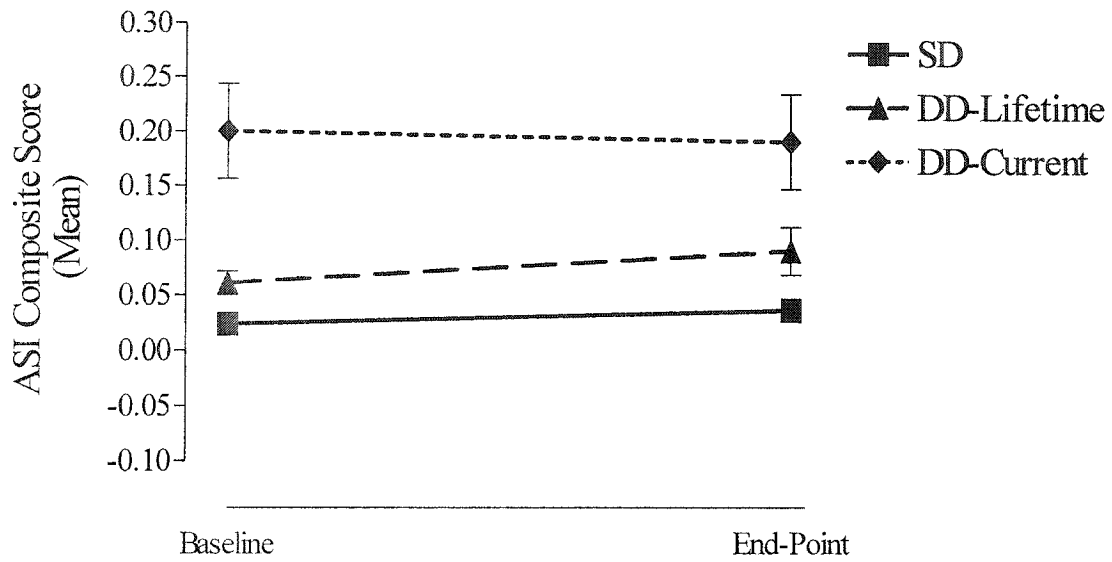


Figure 2: Change in Addiction Severity Index Drug Composite Scores

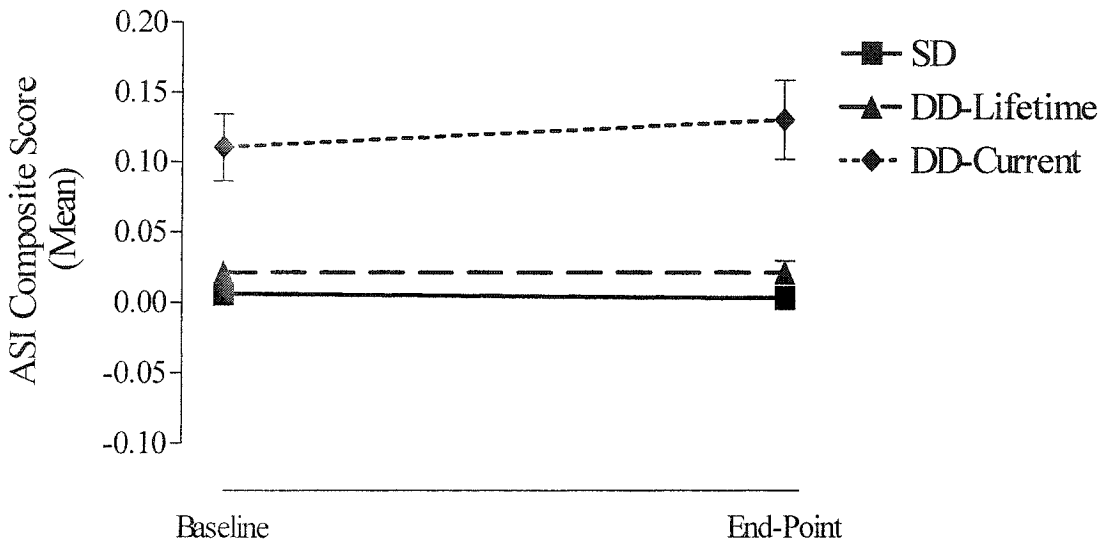


Figure 3:
PANSS Positive by group

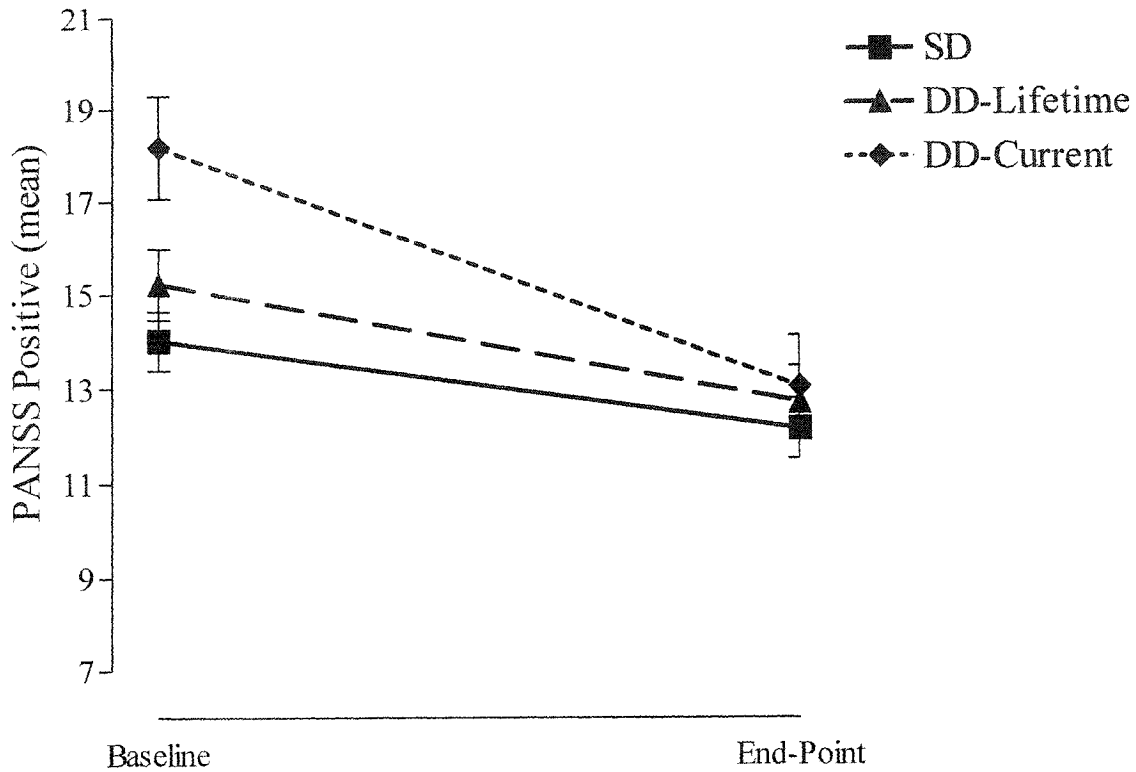


Figure 4: Brief Symptom Inventory-Global Severity Index

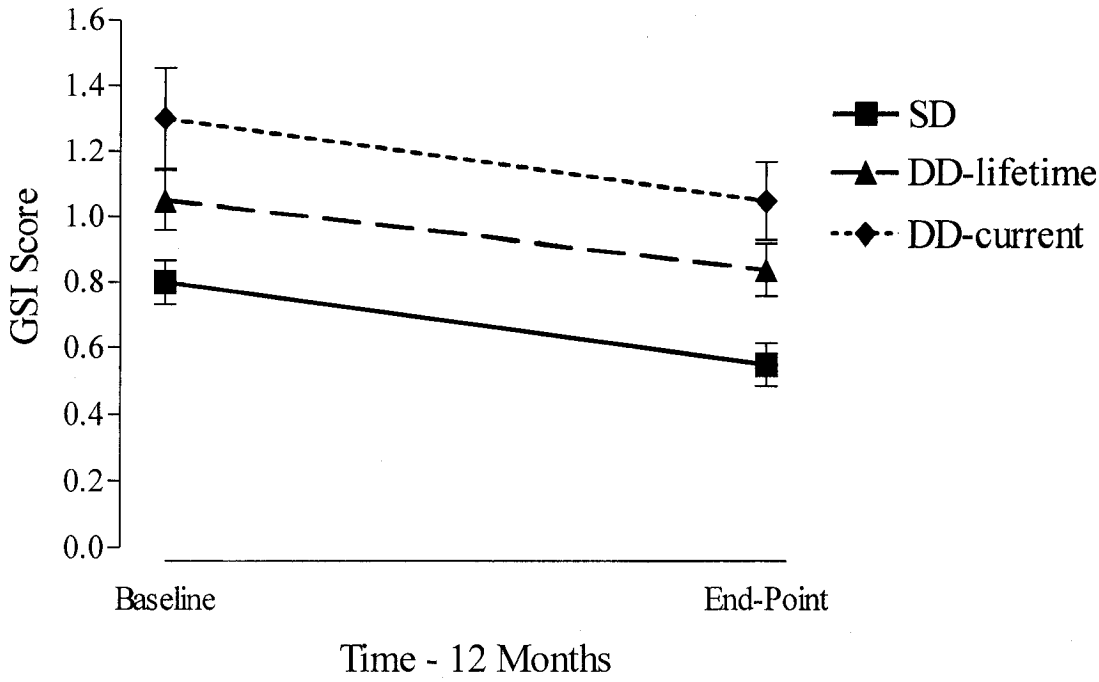
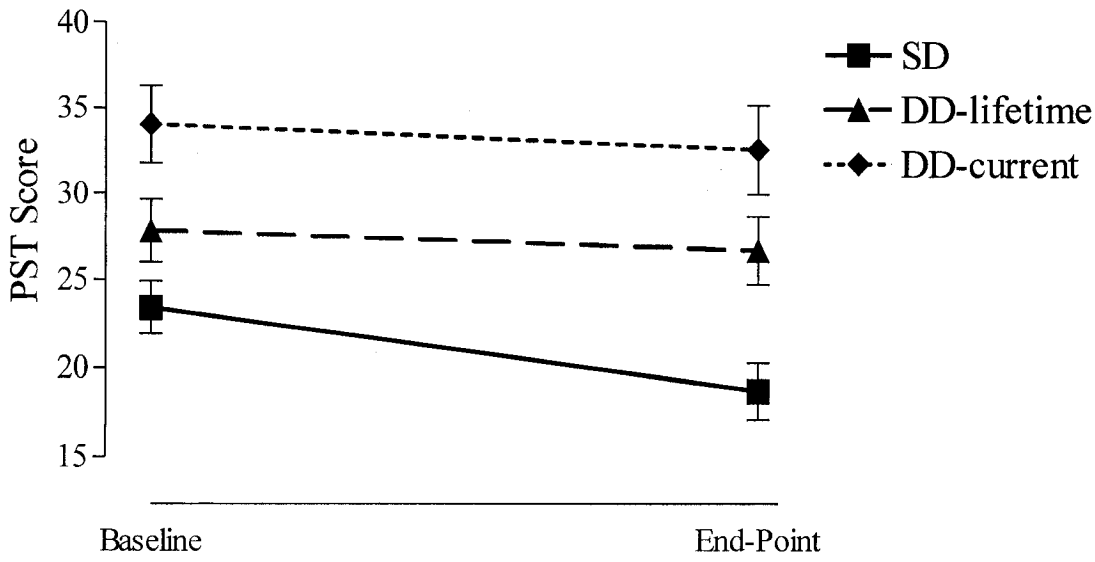


Figure 5: Brief Symptom Inventory-Positive Symptom Total



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Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences

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Abstract

Patients with schizophrenia and related psychoses frequently use, abuse and become dependent on psychoactive substances. Local surveys indicate differences in both types and patterns of substances used. A cross-sectional survey was conducted to document abuse in 207 successive outpatients presenting to a psychiatric continuing care facility in a large Canadian city. Nicotine, alcohol and cannabis were the most frequently abused substances in the cohort. Excluding nicotine, 44.9% met criteria for lifetime and 14.0% for current abuse/dependence. Cocaine, heroin, hallucinogen, amphetamine, and inhalant use were rarely reported. Patients with current substance abuse/dependence and a psychotic disorder (dual diagnosis, DD) had significantly higher Positive and Negative Symptom Scale (PANSS) positive scores than lifetime-DD or those with a single diagnosis (SD). Significantly more current-DD (69.0%) patients were depressed (HAM-D score $\geq$12) compared to SD (45.6%). Furthermore, current-DD (27.6%) patients were more likely than SD (4.5%) to be medication non-compliant.

Patients with current-DD were more likely to smoke cigarettes (88.9%) compared to those with SD (49.6%) and they had significantly longer histories of cigarette smoking (19.1 for DD vs. 11.5 years for SD). The smoking behavior of the DD population is discussed in terms of enhanced risk for alcohol abuse, as well as effects on antipsychotic blood levels and metabolism.

Keywords: Dual diagnosis; Comorbidity; Schizophrenia; Schizoaffective disorder; Substance abuse; Alcohol; Cannabis; Nicotine

Dual diagnosis (DD), the co-occurrence of a mental and addictive disorder, is a common problem for patients with schizophrenia and related psychotic disorders. Previous studies have estimated the prevalence to range from 6% to 60% (Fowler et al., 1998). The Epidemiological Catchment Area study found that 27.5% of patients with schizophrenia had a comorbid substance abuse disorder (Regier et al., 1990), while 44.8% of individuals with non-affective psychosis were classified as DD in the National Comorbidity Survey (Kendler et al., 1996).

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Variation in rates of abuse/dependence among psychotic patient stems from differences in sample size, subject selection, diagnostic criteria, and definitions of substance use disorders. Prevalence of current abuse/dependence in psychiatric inpatients ranges from 12% to 60% (Brady et al., 1991; Cantwell et al., 1999; Havassy and Arns, 1998), and from 48% to 64% for lifetime abuse/dependence (Brady et al., 1991; Dixon et al., 1991). Among outpatients, rates of lifetime and current abuse/dependence vary from 6% to 60% (el Guebaly and Hodgins, 1992; Fowler et al., 1998; Gogek, 1991).

Nicotine, alcohol, cannabis and cocaine are the most commonly used substances by patients with psychotic disorders. In the United States about one-quarter of the population are smokers (Hymowitz et al., 1997), while more than 70% of patients with schizophrenia are nicotine dependent (Van Dongen, 1999; Zeidonis and George, 1997). Alcohol is used by approximately 45–60% of current and former psychotic inpatients (Dixon et al., 1991; Drake et al., 1989, 1993; Hambrecht et al., 1996). While cannabis use is common among the DD population in the United States (31–42%) (Dixon et al., 1991), it is less common in France (27%) (Dervaux et al., 2001), England (18.7%) (Duke et al., 2001) and Germany (5–13%) (Hambrecht and Hafner, 2000; Soyka et al., 1993). Finally, 15–50% of patients with schizophrenia in the U.S. have reported cocaine abuse (Schneier and Siris, 1987; Ziedonis et al., 1992), compared to 1.5% of patients in Australia (Fowler et al., 1998), and 1% in France (Dervaux et al., 2001). In England 8.7% reported lifetime stimulant abuse including cocaine and amphetamines (Duke et al., 2001). Such variance across different social settings underscores the need for local surveys to explore the extent and nature of problems related to DD.

DD patients present more difficulties from a diagnostic and clinical management perspective than single diagnosis (SD) patients. Increased aggression and violence (Angermeyer, 2000; Soyka, 2000) and medication noncompliance (Swartz et al., 1998) have been reported among DD patients (Kamali et al., 2001; Olfson et al., 2000). In a review, Angermayer (2000) found that patients with schizophrenia had a mean odds ratio for violent behaviour of 3.9–8.0 compared to people without mental health problems. However, DD patients were more likely to commit violent offences (mean OR = 7.2–18.8), and were 17 times more likely to commit homicide compared to the general population. Soyka (2000) found that DD patients were more likely to be convicted of criminal activity compared to SD patients (40.1% vs. 13.7%).

Substance use has been found to exacerbate psychiatric symptoms and especially the positive symptoms of schizophrenia. Schizophrenics who abuse alcohol reported significantly more hallucinations and depressive symptoms than nonalcoholic schizophrenics (Pulver et al., 1989), and heavy alcohol use was significantly correlated with hostile threats, paranoia, disorganized incoherent speech, depression and suicidal behaviour (Drake et al., 1989). Continuous delusions were more frequently reported among current cannabis using schizophrenics (43%) compared to past users (21%) or non-users (11%) (Negrete et al., 1986). This study also found similar trends for continuous hallucinations (29% current; 18% past; 6% non-users) (Negrete et al., 1986). Similarly, cannabis-abusing schizophrenics were found to have significantly more hostility and thought disturbance than schizophrenics who did not use cannabis (Caspari, 1999). Patients with schizophrenia who abused cocaine were significantly more likely to have current major depression (Brady et al., 1990) and suicidal ideation (Seibyl et al., 1993). Patients with a cocaine abuse history were more likely to be depressed, less socialized and had more impairment on memory tasks (Sevy et al., 1990). Taken together, these studies point to the negative additive effects of comorbid substance use among psychotic patients, leading to exacerbation or continued psychosis, and poorer social functioning.

Most previous dual diagnosis studies have been conducted in the United States. The present study was conducted in Quebec, Canada. This province is distinct culturally and linguistically and the legal drinking age is 18. (In most North American jurisdictions the legal drinking age is 19 or 21.) The present study used standardized instruments to confirm the diagnosis of psychotic and substance use disorders, measure psychiatric symptoms, and ascertain current patterns of substance use. This study presents data collected at the start of a 12-month longitudinal survey and explores the impact of substance abuse on psychiatric symptoms measured at intake.

1. Methods

1.1. Research site and subjects

The research was conducted in the psychiatry department of the Montreal General Hospital (MGH), a large tertiary care hospital in central Montreal. All new patients presenting to the Continuing Care Service (CCS) of the outpatient department were informed of the project during their initial clinic assessment interview. The CCS serves a population of patients with chronic or recurring psychosis (schizophrenia and related psychoses) from a defined geographical catchment area. The catchment area (defined by home postal code) required patients to obtain all psychiatric services and follow-up at the MGH. The MGH catchment area is wide, representing a multicultural population from both inner city and suburban regions with variation in terms language and socio-economic status. Patients with acute and first episode psychoses were treated at specialized units at another hospital site.

Written informed consent for additional interviews (compensated with $20 in coupons for food, clothing etc), as well as urine toxicology screening and a chart review were requested by the Clinical Research Coordinator. This recruitment procedure resulted in an 80.2% participation rate overall; 14% refused consent and an additional 5.8% were considered to be unable to give consent and/or unable to participate. Post-hoc analysis failed to demonstrate any significant differences in terms of distribution by gender, age or clinical diagnosis between those that participated vs. those that refused consent. Only patients meeting DSM-IV diagnostic criteria for schizophrenia or related psychoses (schizoaffective, delusional disorder, psychosis NOS) were included in the sample and subsequent analyses presented below. Patients meeting criteria for substance-induced psychosis or bipolar disorder were excluded.

1.2. Instruments used for data collection

The mood, psychotic, and psychoactive substance abuse sections of the Structured Clinical Interview for DSM-IV (SCID-P) were administered. Patients were excluded from the study if the clinical and/or hospital chart diagnosis of schizophrenia or related psychosis was not confirmed by the SCID-P.

Baseline demographics including age, ethnicity, education, marital status, and personal and family psychiatric history were collected. Date of onset of psychiatric symptoms, number and length of previous hospitalizations, and medications prescribed (dose, form, compliance status) were obtained from patient interviews and review of previous hospital charts.

Psychiatric symptomatology was assessed using the Positive and Negative Symptom Scale (PANSS) and the Hamilton Depression Rating Scale (HAM-D), while subjective psychological distress was measured with the Brief Symptom Inventory (BSI). The PANSS is a 30-item standardized instrument that measures positive symptoms (e.g. hallucination, delusions), negative symptoms (e.g. affective blunting, emotional withdrawal), and general symptoms (e.g. motor retardation, anxiety, disorientation) using a semi-structured interview and chart review (Kay et al., 1988, 1989). The HAM-D is a 23-item clinician administered scale that rates cognitive, affective, somatic, and vegetative symptoms of depression (Hamilton, 1960). The BSI is a 53-item self-rating questionnaire that evaluates psychological distress in nine areas (e.g. hostility, depression, somatization, anxiety) over the past week (Derogatis and Melisaratos, 1983). A global severity index (GSI) score is also obtained from the nine dimensions providing an indication of overall distress.

The Addiction Severity Index (ASI) was used to determine current and lifetime drug and alcohol use levels (McLellan et al., 1980, 1985). The ASI was found reliable and valid for assessing drug-related behaviours and consequences in mentally ill patients (Carise et al., 2001; el Guebaly and Hodgins, 1992). It assesses the number of days and routes of administration of specific drug (e.g. cannabis, cocaine, amphetamines, etc.) and alcohol use during the past 30 days, as well as the number of days of drug abstinence and extent of substance abuse treatment.

Tardive Dyskinesia (TD) was evaluated using the Abnormal Involuntary Movement Scale (AIMS) (Lane et al., 1985; Simpson et al., 1979). The AIMS is a 10-item scale assessing individual body movements as well as overall severity.

Table 1
Demographics: single (SD) versus dual diagnosis (DD)

	SD ($n=114$)	DD ($n=93$)
Age (mean years ± S.D.)	39.7 ± 10.5	37.6 ± 10.0
Diagnosis: % Schizophrenia	64.0	59.1
% Schizoaffective disorder	22.8	28.0
% Related Psychotic disorders (psychosis NOS, delusional disorder)	13.2	12.9
% Over age 35	59.6	54.8
% Male	46.5	72.0*
Education: above high school (%)	65.8	55.9
% Married	10.5	10.8
% Employed	5.3	4.3
% On welfare (income from social assistance)	61.4	71.0
% With any DSM-IV mood disorder diagnosis	23.7	29.0
Age first received help (mean years ± S.D.)	24.7 ± 8.2	21.2 ± 8.3*
Age first hospitalized (mean years ± S.D.)	28.5 ± 9.0 ($n=104$)	26.4 ± 8.2 ($n=82$)
Lifetime # of hospitalizations (mean ± S.D.)	4.5 ± 4.6	4.6 ± 5.1
Hospitalizations in last 2 years (mean ± S.D.)	1.2 ± 1.4	1.2 ± 1.6
% With history of medical problems	57.0	56.5
History of current medical problems (%)	40.4	25.0
Living arrangements		
% Alone	28.9	35.5
% Institution	27.2	25.8
% With others	43.9	38.7

S.D. = standard deviation.
* DD group significantly different from SD group, X^2 or Fisher's exact test, $p<0.05$ corrected for multiple comparisons.

1.3. Statistical analysis

Data for each patient across all variables including demographic and diagnostic information was coded and entered into a database using Microsoft Excel®. Statistical analysis was conducted using the microcomputer version 10.0 of SPSS® (SPSS, 2000). Fisher's exact tests and chi-square tests of association were used to assess differences in categorical variables between groups. Comparisons between groups for continuous variables were conducted using independent *t*-tests and Analysis of Variance (ANOVA) techniques, including multivariate tests (MANOVA). Post-hoc tests were performed using *t*-tests with a Bonferroni correction.

2. Results

2.1. Characteristics of the sample

Demographic characteristics of DD and SD populations are shown in Table 1. The cohort was a chronically ill population with approximately 16 years since first diagnosis. The sample was comprised of patients with a primary diagnosis of schizophrenia ($n=128$), schizoaffective disorder ($n=52$) and related psychotic disorders (psychosis NOS, delusional disorder) ($n=27$). Of the 207 patients in the sample, 93 (44.9%) were classified as DD and 114 (55.1%) as SD. Among the 93 DD patients, 29 (31.2% and 14.0% of the entire sample) met DSM-IV criteria for current substance use disorder, while the remaining 64 (68.8%) had a lifetime diagnosis. Other than gender composition and age at first psychiatric treatment, DD and SD patients did not differ significantly on any other socio/demographic variable. Demographic data also did not differ between current-DD and lifetime-DD groups.

Medications prescribed were similar for the two groups (Table 2). However, DD patients were significantly more likely to be non-compliant than SD patients (19.1% vs. 4.5%) with current-DD even more so at 27.6%.

2.2. Substance use, abuse and dependence

In this sample, 65.2% had smoked cigarettes, 47.3% used alcohol, while 20.0% used at least one drug of

Table 2
Prescribed medications and compliance status

	SD ($n=114$)	DD ($n=93$)
Antipsychotics		
Typical only (%)	43.0	46.2
Atypical only (%)	41.2	33.3
Both (%)	11.4	14.0
% Depot antipsychotics	18.4	21.5
Any anti-mania medication (%)	21.9	28.0
Any antidepressant (%)	17.5	23.7
Any benzodiazepine (%)	43.9	40.9
Any EPS medication (%)	35.1	43.0
Non-compliant with medications (%)	4.5	19.1*

SD = Single diagnosis, DD = Dual diagnosis, EPS = Extrapyramidal symptom.
* DD group significantly different from SD group, $p<0.05$ corrected for multiple comparisons.

Table 3
Current use of substances (past month)

Substance	No use	Some use		DSM-IV diagnosis of abuse/dependence	
	%	%	Days used past month	%	Days used past month
Alcohol	52.7	37.2	3.5 ± 3.9	10.1	7.3 ± 7.2
Cannabis	87.9	3.9	2.8 ± 2.4	8.2	14.7 ± 11.4
Cocaine	96.1	1.0	1.5 ± 0.7	2.9	4.2 ± 4.0
Benzodiazepines	92.2	6.3	5.8 ± 8.1	1.5	2.7 ± 2.1
Amphetamines	99.5	0.0	–	0.5	30.0 ± 0.0
Hallucinogens	99.5	0.5	1.0 ± 0.0	0.0	–
Prescribed narcotics	98.5	0.5	3.0 ± 0.0	1.0	14.0 ± 8.5
Inhalants	99.5	0.0	–	0.5	25.0 ± 0.0
Heroin	99.5	0.0	–	0.5	2.0 ± 0.0
Barbiturates	99.5	0.0	–	0.5	10.0 ± 0.0
Nicotine[a]	34.8	6.8	8.2 ± 8.0	58.4	30.0 ± 0.0
Caffeine[a]	8.7	22.2	10.5 ± 7.8	69.1	30.0 ± 0.0

Values are expressed as the % of subjects using each substance and the mean ± S.D. number of days used in the past month.
[a] For nicotine and caffeine dependence was defined as daily use.

abuse excluding alcohol, within the previous 30 days. Cannabis was the most commonly used drug (12.1%), followed by benzodiazepines (7.8%; defined as using more benzodiazepines than prescribed) while only 3.9% used cocaine. Other substances were infrequently reported as shown in Table 3. As noted above 14.0% met DSM-IV criteria for current (past month) substance use disorder excluding nicotine and caffeine. Alcohol (10.1%) and cannabis (8.2%) were the most commonly abused substances, followed by cocaine (2.9%) benzodiazepines (1.5%) and opiates (1.0%).

Rates of current alcohol and drug use by diagnostic sub-group are shown in Table 4. Not surprisingly, significantly more current-DD subjects used both alcohol and drugs. It was notable that smoking was much more pervasive among both current (88.4%) and lifetime (84.1%) DD subjects; while 49.6% of SD patient smoked at least one cigarette in the previous 30 days. Current-DD patients used alcohol, drank to intoxication, and used cannabis significantly more often in the previous 30 days than both SD and lifetime-DD subjects.

Table 4
Current use of substances (past month) by diagnostic sub-group

Substance	SD ($n=114$)	DD-current ($n=29$)	DD-lifetime ($n=64$)
Alcohol: % using	36.8	89.3*	46.0
Days used (mean ± S.D.)	1.0 ± 2.13	7.44 ± 7.72*,†	1.53 ± 2.33
Days intoxicated (mean ± S.D.)	0.2 ± 0.9	5.44 ± 8.18*,†	0.43 ± 1.12
Cannabis: % using	0	66.7*	11.1
Days used (mean ± S.D.)	0	9.3 ± 11.42*,†	0.33 ± 1.23
Cocaine: % using	0	18.5*	4.8
Days used (mean ± S.D.)	0	0.56 ± 1.94*	0.21 ± 1.15
Nicotine: % using	49.6	88.9*	84.1*
Days used (mean ± S.D.)	12.36 ± 14.67	26.67 ± 9.61*	24.13 ± 14.49*
Caffeine: % using	90.2	96.3	90.5
Days used (mean ± S.D.)	21.88 ± 11.86	27.41 ± 7.41	23.43 ± 11.57

SD = Single diagnosis, DD = dual diagnosis, S.D. = standard deviation.
* DD-Current or DD-Lifetime groups significantly different from SD group, $p<0.05$.
† DD-current significantly different from DD-lifetime group, $p<0.05$. Corrected for multiple comparisons.

Over the month prior to assessment, current-DD patients spent significantly more money on both alcohol (DD = $58.54 ± 124.60 vs. SD = $3.28 ± 12.0, $p < 0.001$) and drugs (DD=$53.17 ± 73.72 vs. SD = $0.26 ± 2.08, $p < 0.001$) compared to the SD group. These amounts are considerable given that 71.0% of the DD patients were on social welfare, which provides them with $537–776 per month for all expenses.

Lifetime-DD and current-DD patients had longer histories of drinking to intoxication and cannabis use compared to SD (Table 5). History of cocaine and cigarette use was significantly longer for current-DD compared to SD patients.

2.3. Psychiatric symptomatology

Current-DD patients had significantly higher PANSS positive psychotic scores than both lifetime-DD and SD patients (Table 6). While there were no significant group differences on the mean total HAM-D scores, patients with current-DD were more likely to have HAM-D scores in the depressed range of 12 or more (69.0%) compared to DD-lifetime (46.9%) and SD patients (45.6%). Patients with current-DD reported more symptoms on the BSI in terms of the GSI compared to SD subjects, and the PST compared to both SD and DD-lifetime patients. There were no between group differences on either the total or individual items of the AIMS or in expression of symptoms related to prescribed antipsychotic type (data not shown).

Table 5
Lifetime drug use by diagnostic sub-group

Years of substance use (mean ± S.D.)	SD (n=104)	DD-current (n=25)	DD-lifetime (n=53)
Alcohol	15.95 ± 13.92	20.32 ± 9.64	16.88 ± 12.53
Alcohol intoxication	1.41 ± 3.79	11.44 ± 11.58*,†	5.36 ± 6.71*
Benzodiazepine abuse	0.29 ± 2.94	1.56 ± 4.36	0.15 ± 0.63
Cocaine	0.27 ± 2.12	2.32 ± 3.48*	1.26 ± 3.62
Cannabis	0.26 ± 1.01	8.40 ± 8.39*	5.78 ± 7.27*
Cigarettes	11.51 ± 14.16	19.12 ± 11.19*	16.40 ± 11.06
Caffeine	21.04 ± 13.88	22.84 ± 12.89	17.19 ± 14.19

SD = Single diagnosis, DD = dual diagnosis, S.D. = standard deviation.

* DD-current or DD-lifetime group significantly different from SD group, $p < 0.05$.

† DD-current significantly different from DD-lifetime group, $p < 0.05$. Corrected for multiple comparisons.

Table 6
Psychiatric symptomatology: mean scores on the Positive and Negative Symptom Scale (PANSS), Hamilton Depression Rating Scale (HAM-D), and Brief Symptom Inventory (BSI)

	SD (n=114)	DD-current (n=29)	DD-lifetime (n=64)
PANSS (mean ± S.D.)			
Positive	14.25 ± 5.09	18.07 ± 5.18*,†	14.70 ± 5.44
Negative	16.71 ± 5.69	15.93 ± 4.96	16.13 ± 5.19
General	30.13 ± 6.56	33.59 ± 7.42	31.16 ± 8.60
Total	61.10 ± 13.77	67.59 ± 13.54	61.98 ± 15.32
HAM-D (mean ± S.D.)			
Mood	3.5 ± 2.7	5.0 ± 2.8	3.9 ± 2.9
Cognitive	1.7 ± 2.2	2.2 ± 2.7	2.3 ± 2.8
Vegetative	5.1 ± 3.3	6.4 ± 3.3	5.5 ± 3.6
Mania	4.1 ± 2.8	5.6 ± 3.1	4.7 ± 3.2
Total	12.0 ± 7.2	15.1 ± 7.4	13.4 ± 9.0
BSI (mean ± S.D.)			
GST	0.8 ± 0.7	1.3 ± 0.8*	0.9 ± 0.8
PST	23.8 ± 13.0	33.4 ± 13.0*,†	25.6 ± 13.7
PSDI	1.7 ± 0.7	1.9 ± 0.7	1.8 ± 0.7

PANSS = Positive and Negative Syndrome Scale; HAM-D = Hamilton Depression Rating Scale; BSI = Brief Symptom Inventory, GST = global symptom total, PST = positive symptom total, PSDI = positive symptom distress index.

* DD-current or DD-lifetime group significantly different from SD group, $p < 0.05$.

† DD-current group significantly different from DD-lifetime group, $p < 0.05$. Corrected for multiple comparisons.

3. Discussion

In the present study, 44.9% received a DSM-IV diagnosis of substance use disorder. This is comparable to previously reported outpatient samples in the United States, Australia and Europe. Rates of current substance abuse/dependence (14.0%) were lower than previous comparable studies. This is most likely related to use of DSM-IV diagnostic criteria, as well as the fact that current was defined as abuse within the previous 30 days. In the Fowler et al. (1998) study, comparable to the present study in terms of sample size and methods, current use was classified within a 6-month time frame. In their sample, 26.8% (n=194) had a current substance-use disorder. However, defining "current" over a 6-month time frame may be too

long as subjects who have achieved 5 months of abstinence are grouped with those who used the day prior to the survey.

Not surprisingly, the most commonly abused substances were nicotine, alcohol and cannabis. Cigarette smoking was relatively frequent among subjects in the sample with 65.2% reporting some use and 58.4% reporting daily use in the past month. However, the level of smoking in the present sample appears lower than other studies where 70–90% were found to be nicotine dependent (Van Dongen, 1999; Zeidonis and George, 1997). The finding that only 49.6% of SD patients had used nicotine in the past month is indeed important and may reflect the fact that non-smoking patients with schizophrenia are more likely to be health conscious (Zeidonis and George, 1997). Nicotine's ability to temporarily normalize auditory evoked potential deficits in some but not all schizophrenics, possibly via the alpha7 subunit of the nicotinic acetylcholine receptor has also been suggested as a reason for the high rate of nicotine dependence among some patients with schizophrenia (Adler et al., 1998). Importantly, current-DD subjects had significantly longer histories of smoking cigarettes than SD patients (19.1 ± 11.2 vs. 11.5 ± 14.2 years), suggesting that early cigarette use may serve as a risk factor or marker of future involvement with other substances of abuse among patients with schizophrenia. Among non-psychotic individuals with substance use disorders, nicotine use is closely associated with alcohol intake. For example, the occurrence of alcoholism is substantially increased in smokers compared to non-smokers and up to 95% of alcoholics are concurrent smokers (Difranza and Guerrera, 1990). Furthermore, research suggests that early tobacco use may be associated with increased vulnerability for subsequent alcohol use (Abelson et al., 2002; Hughes, 1995). A study of 3356 male twin pairs found a substantial genetic correlation ($r=0.68$) between nicotine and alcohol dependence (True et al., 1999), suggesting that overlapping genetic factors contribute to the clinical and epidemiological associations. Common genetic vulnerability is only one possible mechanism however, and the association between alcohol and nicotine may also be due to shared risk factors (i.e. self-medication of psychological distress), which may be especially prevalent in the DD population.

Smoking can alter medication blood levels making pharmacological interventions quite complex. Certain agents in tobacco smoke increase the metabolism of antipsychotic medications through induction of hepatic cytochrome (CYP) *P*450 enzymes and especially CYP450 1A2 (Nemeroff et al., 1996; van der and Steijns, 1999). For example, clozapine levels increased by a mean 57.4% upon smoking cessation in one study with 11 patients (Meyer, 2001). Additionally, olanzapine clearance is 37–48% lower in non-smokers as compared to smokers (Callaghan et al., 1999). Patients with DD who smoke at a higher rate than SD patients may eliminate their medications faster, and subsequently experience a higher rate of psychiatric impairment. In this study, the DD groups smoked on more days (DD current 26.7 ± 9.6; DD lifetime 24.1 ± 14.5) than the SD group (12.4 ± 14.7) over the past month. Although plasma levels of antipsychotics were not measured, the higher rate of smoking may have contributed to increased impairment in the DD groups.

Alcohol was used by 47.3% of the cohort, while 10.1% had a history of alcohol abuse/dependence. Cannabis was used by 13.1%, with abuse/dependence diagnosed in 8.2% of the cohort. These rates are lower than previous similar studies where 12.3–50% had histories of alcohol abuse/dependence (Alterman et al., 1981; Drake et al., 1990) and 12.5–35.8% had cannabis abuse/dependence histories (Barbee et al., 1989; Cohen and Klein, 1970; Fowler et al., 1998). Cocaine was used by 3.9% of the sample, but only 2.4% had current abuse/dependence. This finding is more similar to the experiences in Australia where 1.5% reported cocaine use in the previous 6 months (Fowler et al., 1998), and France where 1% reported lifetime cocaine abuse (Dervaux et al., 2001), as compared to the US where 10–15% of patients abuse cocaine (Dixon et al., 1991).

In the present cohort, positive psychotic symptoms were greatest for the current-DD group. This suggests that substance abuse affects positive but not negative symptoms of schizophrenia. It is possible that the increased psychopathology can be accounted for by increased medication noncompliance among current-DD subjects (27.6%), vs. 15.0% among lifetime-DD and 4.5% among SD patients. This finding validates previous literature examining non-compliance in psychotic patients with DD (Fenton et al.,

1997; Heyscue et al., 1998; Swartz et al., 1998). For example, Kamali et al. (2001) used logistic regression analysis to find that current comorbid substance misuse and poorer insight into illness were significantly associated with poor antipsychotic compliance among patients ($n=66$) with schizophrenia or schizoaffective disorder. In a larger sample ($n=213$) of patients with schizophrenia or schizoaffective disorder, substance use (OR=4.6, CI=1.7–12.0), history of noncompliance (OR=4.1, CI=1.3–12.2), and family refusal to participate in treatment (OR=3.4, CI=1.1–10.3) significantly predicted medication noncompliance in the first 3 months after hospital discharge (Olfson et al., 2000).

All antipsychotic medications are dopamine receptor (D_2) blockers while drugs of abuse are direct or indirect dopamine agonists. Breen and Thornhill (1998) suggest that DD patients become non-compliant through two mechanisms: (1) antipsychotic blockade of dopamine mediated euphoria from the drug of abuse and (2) lack of efficacy of antipsychotic due to ongoing substance use with consequent loss of faith in the treatment. In the present study, lifetime-DD and SD patients had equivalent levels of positive psychopathology despite unequal rates of non-compliance, arguing for a direct role of current substance use, for example cigarette smoking as detailed above, in increasing positive symptoms of schizophrenia.

Clinically significant depression as measured by the HAM-D was more frequent among current-DD patients compared to the other two groups. This may be related to self-medication, as depressed persons may be more likely to use licit and illicit substances to alleviate depressed mood, and/or to a direct depressant effect of the substances of abuse.

Limitations of the current study include the cross-sectional design in which psychiatric symptoms were measured at one point in time. Since psychiatric symptoms vary and are likely to vary with the patterns of current substance use, the relationship between use and expression of psychiatric symptoms could not be explored in this study. As well clinical samples are by their nature biased. However, this was a sample from a large catchment area and the refusal rate of the sample (14%) was relatively low. Furthermore, this study relied on self-report data, which underestimates medication non-adherence as well as current substance abuse; thus some SD patients may have been incorrectly classified as SD instead of DD.

In conclusion, the present cohort of patients with schizophrenia and schizoaffective disorder from an urban Canadian center reported lower rates of substance use and, abuse/dependence compared to studies conducted in the United States. It is not clear why this would be the case but more comprehensive social welfare and medical care coverage may in part explain these findings. In this study, current nicotine use was related to use of other substances of abuse, so its use may reflect a more general predisposition to drug dependence among schizophrenics. Finally, current-DD patients have significantly elevated rates of medication non-compliance, positive psychotic symptoms, clinically significant depression, and cigarette smoking compared to SD patients.

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