



ELSEVIER

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Schizophrenia Research 66 (2004) 125–135

SCHIZOPHRENIA
RESEARCH

www.elsevier.com/locate/schres

First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol

Alan I. Green^{a,b,*}, Mauricio F. Tohen^c, Robert M. Hamer^d, Stephen M. Strakowski^e,
Jeffrey A. Lieberman^d, Ira Glick^f, W. Scott Clark^c
HGDH Research Group¹

^aCommonwealth Research Center and the Massachusetts Mental Health Center, Harvard Medical School, 74 Fenwood Road, Boston, MA 02115, USA

^bDartmouth Medical School, One Medical Center Drive, Lebanon, NH 03756, USA

^cEli Lilly and Co, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, USA

^dDepartment of Psychiatry #7160, 7025 Neurosciences Hospital, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

^eUniversity of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0559, USA

^fStanford Medical School, PBS #2200, Stanford, CA 94305, USA

Received 21 January 2003; received in revised form 29 July 2003; accepted 2 August 2003

Abstract

Background: Co-occurring substance use disorders, mostly involving alcohol, cannabis or cocaine, occur commonly in patients with schizophrenia and are associated with increased morbidity and mortality. Available but limited data suggest that substance use disorders (especially cannabis use disorders) may also be common in first-episode patients and appear linked to a poor outcome in these patients. Strategies to curtail substance use form an important dimension of the treatment program for both first-episode and chronic patients. We report on rates of co-occurring substance use disorders in patients within their first episode of schizophrenia-related psychosis from a multicenter, international treatment trial of olanzapine vs. haloperidol.

* Corresponding author. Dartmouth Medical School, One Medical Center Drive, Lebanon, NH 03756, USA. Tel.: +1-603-650-7549; fax: +1-603-650-8415.

E-mail address: Alan.I.Green@Dartmouth.edu (A.I. Green).

¹ HGDH Research Group: This paper was based (in part) on results from the study of the *Comparative Efficacy And Safety Of Atypical And Conventional Antipsychotic Drugs In First-Episode Psychosis* by the HGDH Study Group sponsored by Eli Lilly and Company. The HGDH research group consists of Drs. Jeffrey A. Lieberman and Diana Perkins, Dept. of Psychiatry Univ. of North Carolina School of Medicine, NC, USA; Drs. Joseph P. McEvoy, Cecil Charles and Richard Keefe, John Umstead Hospital, Duke University Health System, NC, USA; Drs. Robert B. Zipursky and Zafiris J. Daskalakis, Dept. of Psychiatry, University of Toronto School of Medicine, Ontario, Canada; Dr. Alan I. Green, Massachusetts Mental Health Center, Harvard Medical School, MA, USA; Dr. Charles B. Nemeroff, Dept. of Psychiatry, Emory University School of Medicine, GA, USA; Prof. Robin Murray and Dr. Tonmoy Sharma, Institute of Psychiatry, UK; Dr. Raquel E. Gur, Dept. of Psychiatry Univ. of Pennsylvania Medical Center, PA, USA; Drs. Bruce Cohen and Franca Centorrino, McLean Hospital, Harvard Medical School, Belmont MA, USA; Prof. Dr. R.S. Kahn, University Hospital, Utrecht, The Netherlands; Drs. Wayne Goodman and John Kuldau, Dept. of Psychiatry, Univ. of Florida, FL, USA; Drs. Anthony J. Rothschild and Jayendra K. Patel, Dept. of Psychiatry, Univ. of Massachusetts Medical Center, MA, USA; Dr. Stephen M. Strakowski, Dept. of Psychiatry, Univ. of Cincinnati, OH, USA; Dr. Ira Glick, Dept. of Psychiatry, Stanford University School of Medicine, CA, USA; Dr. John De Quardo, Dept. of Psychiatry, Univ. of Michigan Medical Center, MI, USA; Drs. Gary Tollefson, Todd Sanger, Mauricio Tohen, Lilly Research Laboratories, IN, USA.

Methods: The study involved 262 patients (of 263 who were randomized and who returned for a post-randomization evaluation) within their first episode of psychosis (schizophrenia, schizoaffective disorder or schizophreniform disorder) recruited from 14 academic medical centers in North America and Western Europe. Patients with a history of substance dependence within 1 month prior to entry were excluded. **Results:** Of this sample, 97 (37%) had a lifetime diagnosis of substance use disorder (SUD); of these 74 (28% of the total) had a lifetime cannabis use disorder (CUD) and 54 (21%) had a lifetime diagnosis of alcohol use disorder (AUD). Patients with SUD were more likely to be men. Those with CUD had a lower age of onset than those without. Patients with SUD had more positive symptoms and fewer negative symptoms than those without SUD, and they had a longer duration of untreated psychosis. The 12-week response data indicated that 27% of patients with SUD were responders compared to 35% of those without SUD. Patients with AUD were less likely to respond to olanzapine than those without AUD. **Discussion:** These data suggest that first-episode patients are quite likely to have comorbid substance use disorders, and that the presence of these disorders may negatively influence response to antipsychotic medications, both typical and atypical antipsychotics, over the first 12 weeks of treatment.

© 2003 Elsevier B.V. All rights reserved.

Keywords: Psychosis; First episode; Substance use disorder; Alcohol; Marijuana; Olanzapine; Haloperidol

Schizophrenia is a relapsing disorder that produces profound effects. Early in its course, frequent exacerbations and florid symptoms may occur; later on, severe disability may develop (McGlashen and Fenton, 1993). Suicide is disturbingly common in schizophrenia, occurring in 10% of patients with the disorder, including those in the early years of illness (Harkavy-Friedman and Nelson, 1997; Tsuang, 1978; Tsuang et al., 1999; Lindelius and Kay, 1973; Roy et al., 1984; Wilkinson, 1982). Co-occurring substance use disorders (mostly involving alcohol, cannabis or cocaine), a common concomitant of chronic schizophrenia, are associated with increased morbidity and mortality (Harkavy-Friedman and Nelson, 1997; Soyka et al., 1993; Allebeck et al., 1987; Negrete et al., 1986; Soni and Sobell, 1991; Osher and Kofoed, 1989; Drake and Brunette, 1998). Available but limited data suggest that substance use disorders (especially cannabis use disorder) may also be common in first-episode patients, appear linked to a poor outcome in these patients, and may be factors in patients' long-term deterioration (Grech et al., 1999; Kovaszny et al., 1997; Gut-Fayand et al., 2001; Verdoux et al., 1999). Not surprisingly, strategies to curtail substance use form an important dimension of the treatment program for both first-episode and chronic patients (Addington, 1999; Green et al., 2002).

Pharmacotherapy has been a mainstay of treatment for schizophrenia since the introduction of the typical antipsychotic drugs, in the 1950s. Despite the clinical value of these agents, however, not all patients re-

spond to them, and other patients cannot tolerate taking them. Lastly, the medications appear to be of little value in controlling the co-occurring substance abuse frequently present in this population (Bowers et al., 1990).

A growing body of data, however, suggest that a "critical period" exists in patients with schizophrenia during the early years of psychosis, in which symptoms and functioning continue to worsen (Wyatt, 1991; Waddington et al., 1998; Loebel et al., 1992; Haas et al., 1998; Birchwood et al., 1998). Wyatt (1991), based on his review of 22 studies of chronic patients, implied that prolonged and repeated psychotic episodes may be biologically "toxic" and could make subsequent episodes and eventual loss of functioning more likely. Wyatt's article sparked reports (Waddington et al., 1998; Loebel et al., 1992; Haas et al., 1998; Moscarelli et al., 1991) supporting the notion that a long "duration of untreated psychosis" ("DUP") in first-episode patients is associated with a poor outcome, increased symptoms and functional impairment, although not all reports agree (Ho et al., 2000). Moreover, in the years subsequent to Wyatt's article, reports of Olney and Farber (1995) and Sheitman and Lieberman (1998) have provided possible neurobiologic formulations that could account for the observations that continued symptomatology results in decline in long-term outcome in patients.

The work of these and other investigators greatly influenced the nature of on-going research in schizophrenia: there has been a recent emphasis toward

studies of first-episode patients and the general concept of preventive intervention in schizophrenia. The recent availability of the new “novel” antipsychotic drugs, thought to be more effective and generally better tolerated than the typical agents, has even further sparked research in the early phases of schizophrenia. Studies of these new agents in first-episode populations are underway, and preliminary reports are beginning to appear. As part of the assessment of these new novel antipsychotic drugs in first-episode patients, an assessment of their effects, in particular, on those first-episode patients with co-occurring substance use disorders, those likely to have the poorest overall outcome, is of great importance.

One such study has recently been completed—a multicenter international study of the novel antipsychotic olanzapine vs. the typical antipsychotic haloperidol in patients within their first episode of schizophrenia. Data from the first 12 weeks of treatment with these two agents have been published (Lieberman et al., 2003). We report here data regarding the abuse or dependence of substances in this population at the beginning of the study, and we compare the 12-week outcome of patients with a co-occurring substance use disorder to those without such a co-occurring disorder. Our hypothesis was that patients with a co-occurring substance use disorder would have a poorer 12-week outcome than would those without such a co-occurring substance use disorder.

1. Methods

1.1. Study sample

The study was a double-blind, randomized, multisite, international 2-year study of olanzapine vs. haloperidol in 262 patients with first-episode psychosis (meeting DSM-IV criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder) recruited from 14 academic medical centers in North America and Western Europe. (Note: 263 were randomized and 262 returned for a post-randomization evaluation). The sample was ascertained from patients (age 16 to 40) who presented to clinical services for evaluation and treatment of psychosis. Diagnostic inclusion criteria included schizophrenia,

schizoaffective disorder or schizophreniform disorder, according to DSM-IV as assessed using SCID-IV, Research Version (First et al., 1996). At entry, patients had to have a score on at least two PANSS psychosis items of ≥ 4 , or a score on one psychosis item of ≥ 5 , and a CGI score ≥ 4 (moderately ill). By history, patients could not have been psychotic for longer than 5 years, and there could not be evidence of recovery from the initial episode for a period of 6 months or longer. Previous treatment with antipsychotic medications was allowed, but for no more than 16 cumulative weeks; patients with a previous trial of clozapine or those treated with an injectable depot neuroleptic within 3 months of study entry were excluded. Lastly, patients with a history of DSM-IV substance dependence (except caffeine and nicotine dependence) within 1 month prior to entry were excluded. A detailed description of the full study inclusion and exclusion criteria is available elsewhere (Lieberman et al., 2003).

1.2. Study design

Patients who were competent and signed an informed consent underwent a neuroleptic washout period of 2 to 14 days (if they had been taking antipsychotics prior to entry), following which they were randomized to treatment with olanzapine or haloperidol. The study was divided into a 12-week acute treatment phase and a 92-week continuation phase. During the acute treatment phase, the initial dose titration ranges for the first 6 weeks were olanzapine 5–10 mg/day and haloperidol 2–6 mg/day; for the second 6 weeks of the acute phase, the allowed doses were olanzapine 5 to 20 mg/day and haloperidol 2 to 20 mg/day. During the acute phase of the study, chloral hydrate (500 to 2000 mg/day), lorazepam (1 to 8 mg/day) or diazepam (5 to 40 mg/day) could be given for the management of agitation, general behavior and/or insomnia for a cumulative duration of no greater than 21 days. Antiparkinsonian medications were allowed if clinically significant EPS occurred: allowed medications included anticholinergics (bentropine or biperiden up to 6 mg/day), propranolol (10 to 80 mg/day), or procyclidine (oral or intramuscular administration of 5 to 10 mg, two to three times daily, for a maximum dose of 30 mg/day). Antidepressants

and mood stabilizers were not permitted during the acute phase of the study. A full description of the study design has been provided elsewhere (Lieberman et al., 2003).

1.3. Assessments

1.3.1. Efficacy

Within the study, efficacy was measured in four domains: (1) psychopathology; (2) psychosocial measures of social and vocational function and quality of life; (3) neurocognitive function; and (4) brain morphology and metabolism. Only results of psychopathology will be reported in this article. Psychopathology was assessed (weekly through week 6 and biweekly through week 12) by the PANSS (30 items, 1–7 severity scale), MADRS (10 items, 0–6 severity scale), and CGI severity item (severity scale 1–7). Patients who met the following criteria were classified as treatment responders: (1) no rating of >3 (mild) on items P1, P2, P3, P5 and P6 of the PANSS; (2) $\geq 30\%$ reduction from baseline in PANSS total score; and (3) CGI severity score < 4 (moderately ill).

1.3.2. Safety

The complete safety assessment battery is described elsewhere (Lieberman et al., 2003). Vital signs were measured at each study visit. EPS and abnormal involuntary movements were assessed by examinations of patients and scored on the Simpson Angus Scale, the AIMS and the Barnes Akathisia Scale at every assessment visit.

1.3.3. Substance use

Patients were assessed at baseline (with the SCID) to determine whether there was a lifetime history or current evidence of alcohol or other substance use disorder (abuse or dependence). Information was available for substance (including alcohol) use disorder (SUD), alcohol use disorder (AUD), cannabis use disorder (CUD), cocaine use disorder (COUD), and hallucinogen use disorder (HUD).

1.3.4. Duration of untreated psychosis

Duration of untreated psychosis (DUP) was calculated as the number of months between the time of onset of psychotic symptoms and the time of onset of treatment with an antipsychotic medication.

1.3.5. Statistical analysis

Baseline descriptive statistics were calculated using means and standard deviations for continuous variables and frequencies for categorical variables. Group differences between SUD and Non-SUD groups, AUD and Non-AUD groups, and CUD and Non-CUD groups were done using *t*-tests for continuous variables and Chi-Squared statistics for categorical variables. Such tests should be interpreted with caution due to multiple comparison issues. Tests on 12-week responder status were done in the context of three two-factor logistic regression models (for SUD, AUD, and CUD) with treatment (haloperidol vs. olanzapine) and substance use status, and their interaction, as the factors, and response status as the response variable. Main effects for the two factors and their interaction were tested using Wald tests due to the large sample size. Simple effects were tested where appropriate (in the presence of a significant main effect and a sizable interaction) using Wald tests. Continuous response variables were tested using a two-factor ANOVA model.

2. Results

Of the sample of 262 patients, 97 (37%) had a lifetime DSM-IV substance use disorder (SUD) diagnosis; 20 patients (7.6%) had a lifetime DSM-IV substance use disorder diagnosis with evidence of current use (prior to hospitalization). If assessed by particular substance, 74 (28%) of the patients had a lifetime cannabis use disorder (CUD); 54 (21%) had a lifetime diagnosis of alcohol use disorder (AUD); 17 (6%) had a lifetime diagnosis of cocaine use disorder; 12 (5%) had a lifetime diagnosis of hallucinogen/PCP use disorder; and 3 (1%) had a lifetime diagnosis of opioid use disorder.

2.1. Baseline characteristics

Descriptive characteristics of those patients with lifetime SUD and those without SUD (non-SUD) are noted on Table 1. The table also includes the characteristics of those patients with and without lifetime cannabis use disorder (CUD) and alcohol use disorder (AUD) diagnoses. (Because the samples of patients with lifetime diagnosis for other substances were so

Table 1
Baseline characteristics

	Substance abuse disorder		Alcohol abuse disorder		Cannabis use disorder	
	Yes	No	Yes	No	Yes	No
	<i>N</i> =96	<i>N</i> =166	<i>N</i> =54	<i>N</i> =208	<i>N</i> =74	<i>N</i> =188
Age onset (years)	22.4	22.7	23.3	22.4	21.3	23.04**
Percent male	93	75***	96	78**	92	78**
Percent schizophrenia	57	61	54	61	57	61 [†]
DUP, months	19.5	12.1*	16.4	14.4	20.1	12.7 [†]
PANSS total	81.8	81.8	82	81.8	81.4	82
PANSS positive	22.7	21.2*	22.7	21.6	22.8	21.4*
PANSS negative	19.0	20.3 [†]	18.9	20.4	19	20.1
Simpson Angus	0.7	1.2*	0.7	1.1	0.6	1.2*
Barnes	0.27	0.24	0.26	0.25	0.23	0.26
AIMS	0.19	0.14	0.2	0.14	0.16	0.15
Insight	13.2	12.9	13.1	13.0	12.9	13.1
MADRS total	12.5	11.2	12.5	11.5	12.5	11.4

Baseline characteristics (expressed as mean values) of patients in the study.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

[†] $p < 0.1$.

small, data are not reported for these groups). Patients with substance use disorder, as well as those with AUD and CUD, were more likely to be men than were those without SUD ($p < 0.001$), AUD ($p < 0.01$) or CUD ($p < 0.01$). The age of the subjects at initiation of the study was similar for patients in the various categories of substance use disorder (data not shown in Table). However, regarding age of onset, while patients with SUD or AUD did not differ significantly from those without those diagnoses ($p > 0.1$ for both), patients with a lifetime CUD had a lower age of onset than those without CUD (21.3 vs. 23.04, $p < 0.01$). Lastly, the duration of untreated psychosis was significantly greater for patients with a diagnosis of SUD than for those without such a diagnosis (19.5 ± 26.6 vs. 12.1 ± 14.7 months; $p < 0.05$). As shown in Table 1, DUP was numerically greater in those with AUD or CUD, as compared to those without these diagnoses. While the difference was not significant for AUD, it was of trend significance ($p < 0.08$) for CUD vs. non-CUD.

Efficacy and EPS data for patients rated at baseline are also described in Table 1. In general, while patients with SUD, AUD and CUD had numerically greater PANSS positive scores and numerically lower PANSS negative scores than did patients without these disorders (see Table 1 for p -values), the differ-

ences in positive symptoms were significant only between SUD and non-SUD (22.7 vs. 21.2, $p < 0.05$) and CUD and non-CUD (22.8 vs. 21.4, $p < 0.05$), and the difference in the negative symptom score was significant between SUD and non-SUD (19.0 vs. 20.3, $p < 0.05$). The total score on the Simpson Angus scale was numerically lower for all categories of patients with a substance use disorder (see Table 1 for p -values), although the difference was significant only for SUD vs. non-SUD (0.7 vs. 1.2, $p < 0.05$) and CUD vs. non-CUD (0.6 vs. 1.2, $p < 0.05$).

2.2. Treatment data

The mean modal dose of olanzapine during the 12-week trial was 10.2 mg/day; for haloperidol, the mean modal dose was 4.8 mg/day.

If patients are classified into responders and non-responders at 12 weeks by the a priori definition as described in the Methods, the proportion responding by substance use disorder status and by treatment group can be seen in Table 2. Twenty seven percent of those with SUD were responders (23% for olanzapine and 31% for haloperidol), as compared to 35% of those with non-SUD (38% for olanzapine and 32% for haloperidol).

We assessed the effect of substance use status and treatment on response status using two-factor logistic regression models. We fit three parallel models, one for SUD vs. NON-SUD, one for AUD vs. NON-AUD, and the third for CUD vs. NON-CUD, as specified above in Methods. Table 2 contains the results of these analyses. Neither SUD nor CUD appeared to affect

Table 2
Responder status by treatment group and substance use disorder (N [Percent])

		Responder N (%)	Non-responder N (%)	RR	95% CI
<i>Overall</i>					
Substance use disorder	Yes	26 (27%)	69 (73%)	1.12	(0.94–1.32)
	No	55 (35%)	102 (65%)		
Alcohol use disorder	Yes	10 (19%)	43 (81%)*	1.26	(1.07–1.49)
	No	71 (35%)	128 (64%)		
Cannabis use disorder	Yes	21 (28%)	53 (72%)	1.08	(0.90–1.29)
	No	60 (34%)	118 (66%)		
<i>Haloperidol</i>					
Substance use disorder	Yes	16 (31%)	35 (69%)	1.01	(0.80–1.29)
	No	24 (32%)	51 (68%)		
Alcohol use disorder	Yes	8 (27%)	22 (73%)	1.10	(0.85–1.42)
	No	32 (33%)	64 (67%)		
Cannabis use disorder	Yes	12 (32%)	25 (68%)	0.99	(0.76–1.28)
	No	28 (31%)	61 (69%)		
<i>Olanzapine</i>					
Substance use disorder	Yes	10 (23%)	34 (77%)	1.24	(0.98–1.57)
	No	31 (38%)	51 (62%)		
Alcohol use disorder	Yes	2 (9%)	21 (91%)*	1.47	(1.21–1.79)
	No	39 (38%)	64 (62%)		
Cannabis use disorder	Yes	9 (24%)	28 (76%)	1.18	(0.92–1.50)
	No	32 (36%)	57 (64%)		

response rate, either overall (main effect) or in either of the two therapy conditions (simple effect), although the risk ratios suggest that patients treated with olanzapine who had a substance use disorder did not respond as well as those diagnosed without such a disorder. In the model predicting response, AUD status significantly affected the probability of a response (Wald $\chi^2 = 5.8650$, $df = 1$, $p < 0.02$). However, the treatment-by-AUD-status interaction approached significance ($p < 0.08$), indicating it might be worthwhile to examine the effect of AUD status on response rates separately for each of the treatments (simple effects). We examined the simple effect of AUD in this model for both the haloperidol and olanzapine groups, and found a significant effect of AUD diagnosis on response rate in the olanzapine group (Wald $\chi^2 = 5.8499$, $df = 1$, $p < 0.02$) but not in the haloperidol group (Wald $\chi^2 = 0.4666$, $df = 1$, $p < 0.49$). While in the haloperidol group, 27% of the AUD subjects were responders, in the olanzapine group only 9% responded.

Table 3 demonstrates the change in symptom ratings over the 12-week period for patients treated with olanzapine or haloperidol, as assessed by total PANSS score. (Note: We present only the results for the PANSS total score, which was the protocol-specified primary response variable, because the multiple comparisons issue raised by examining individual measures, such as the PANSS subscales, the MADRS or the CGI scores, makes interpretation of such tests problematic). The

Notes to Table 2:

Each cell contains the number of patients who fell into a joint response–substance use category. The percentages are the column percentages within each two-by-two table, i.e., the percentages of substance abusers or non-substance abusers who responded and failed to respond. Percentages in each two-by-two table add to 100%. Hypothesis tests were done in each two-by-two table to test whether the column distributions were the same, i.e., was the proportion of subjects who fell into the respond and non-respond categories the same for substance users and non-substance users. These hypotheses tests were done in the context of a two-way factorial logistic regression, where the two factors were drug (haloperidol or olanzapine) and substance use status (lifetime diagnosis), and the dependent variable was response status. Thus, the uppermost set of tables corresponds to the test of the main effect for substance use status in this model, and the remaining two sets of tables correspond to tests of simple effects in this model. Since these tests were not corrected for multiple comparisons, they should be interpreted with caution. Only p -values less than 0.05 are given. In addition, risk ratios (RR) and confidence intervals (95% CI) are noted.

* $p < 0.05$.

Table 3
Treatment and substance use effects on measures of efficacy

Treatment	Substance use	Baseline	Change	<i>p</i> -Value	
		Mean (S.D.)	Mean (S.D.)		
PANSS total					
Olanzapine	SUD	80.98 (13.37)	17.37 (17.65)	0.6091	
	Non-SUD	80.83 (15.37)	19.77 (23.11)		
	AUD	79.87 (14.15)	15.27 (18.12)		0.4919
	Non-AUD	81.11 (14.81)	19.73 (21.98)		
	CUD	80.70 (13.43)	15.94 (17.72)		0.3081
Non-CUD	80.96 (15.20)	20.16 (22.63)			
Haloperidol	SUD	82.65 (17.68)	15.20 (18.42)	0.5743	
	Non-SUD	82.13 (16.95)	18.43 (18.92)		
	AUD	83.80 (16.23)	14.13 (15.59)		0.3226
	Non-AUD	81.89 (17.52)	18.09 (19.58)		
	CUD	82.08 (18.11)	13.44 (18.27)		0.3948
Non-CUD	82.45 (16.88)	18.64 (18.78)			

We indicate *p*-values from an ANOVA contrast between substance use disorder vs. no substance use disorder (or alcohol, or cannabis), within each of haloperidol and olanzapine, with change in PANSS total as the dependent variable, with therapy (haloperidol vs. olanzapine), and the substance use disorder as the predictor variables, in a two-by-two factorial analysis.

trend throughout is for patients with a substance use disorder (whether SUD, AUD or CUD) to have a poorer response than those without a substance use disorder, whether treated with olanzapine or haloperidol, but this effect is nonsignificant. (While not shown, the data are consistent if subdivided into subscales of the PANSS, and for the MADRS or the CGI. The one exception appears to be for the response of positive symptoms to olanzapine treatment, where the difference between the groups does not appear to exist). This trend is consistent with the overall findings as described earlier, when subjects are divided into responders and non-responders.

To examine the relationship of substance use disorder history to compliance with treatment, we fit an ANOVA model predicting compliance (defined for each subject as the proportion of days that the subject took at least one pill of prescribed study medication) from SUD and treatment group (as a potentially mediating variable). Neither treatment group nor the SUD by treatment group interaction had an effect, but those with SUD had a significantly lower proportion of compliant days (87.5%) than did those without a SUD history (93.4%; $F_{1,248} = 5.57$, $p < 0.02$).

To examine the relationship of SUD history to the likelihood of dropout during the trial, we fit a logistic

regression model predicting the likelihood of dropout from SUD history and treatment group (as a potentially mediating variable). In this model, there was a significant treatment group interaction (Wald $\chi^2 = 4.215$, $df = 1$, $p < 0.04$), indicating that the effect of SUD history on likelihood of dropout differed between the treatment groups. For subjects treated with haloperidol, 71% of the subjects with no SUD history completed the study vs. 51% of the subjects with a SUD history (Fisher Exact $p < 0.04$). For subjects treated with olanzapine, however, 71% of the subjects with no SUD history completed the study vs. 77% of the subjects with a SUD history (Fisher Exact $p < 0.53$).

3. Discussion

Data from this study support the notion reported by other investigators (Grech et al., 1999; Kovaszny et al., 1997) that patients within their first episode of schizophrenia-related psychosis quite commonly exhibit co-occurring substance use disorders. This is true for this international sample, even though patients were excluded from the study if they had a recent history of substance dependence. Thus, while 38% of the patients had a lifetime diagnosis of substance use disorder, only 7% had a current substance use disorder. The data suggesting that cannabis use disorder, followed by alcohol use disorder, are the most common substances used by this population are also in line with data from other investigators studying first-episode populations (Rolfe et al., 1999; Addington, 1999; Brewer et al., 1999; Kovaszny et al., 1997; Curry et al., 1999; Hambrecht and Hafner, 1996; Cantwell et al., 1999).

First-episode patients with substance use disorder were more likely to be male (consistent with other studies about patients with chronic schizophrenia and co-occurring substance use disorder (Mueser et al., 1990, 1995)). Our data suggest that patients with lifetime CUD diagnosis have an earlier age of onset of psychosis. This suggests the possibility that cannabis use may be a precipitating factor in the development of psychotic symptomatology in these patients, as suggested by others (Buhler et al., 2002). Furthermore, the finding that duration of untreated psychosis was significantly greater in

patients with SUD, compared to those with non-SUD, is intriguing given the suggestion by some but not all groups that duration of untreated psychosis may be related to patient outcome (Haas et al., 1998; Ho et al., 2000; Loebel et al., 1992; Moscarelli et al., 1991; Waddington et al., 1998). It suggests the possibility that SUD may obscure the diagnosis of schizophrenia and delay the onset of treatment.

At baseline, our patients with SUD appeared to have more positive symptoms, and fewer negative symptoms than did patients without SUD. The different symptom profiles would seem unlikely to be directly caused by substance use itself, since most of these patients were not current abusers, but had a lifetime history of abuse or dependence. Moreover, the finding that negative symptoms were actually less in those with a lifetime SUD than in those without SUD suggests that the theoretical formulation suggesting that patients may try to “self-medicate” negative symptoms (Khantzian, 1985, 1997; Siris, 1990) with substances may not be correct (Green et al., 1999; Buhler et al., 2002; Lammertink et al., 2001; Strakowski et al., 2000).

The trend in our data (even these acute treatment data) supports the notion that patients with substance use disorders (by historical assessment) respond more poorly to treatment than those without such disorders. Perhaps not surprisingly, and possibly related to their relatively poor response, patients with SUD are somewhat less likely to be compliant with taking prescribed medication on a regular basis than are other patients. As a group, patients with SUD (as well as those with AUD and CUD) did not respond as well as those without a history of a substance use disorder on measures of total symptoms, positive symptoms, negative symptoms, general psychopathology, depression and overall functioning. If looked at in terms of those having a predetermined level of treatment response, there is the suggestion that patients with AUD and treated with olanzapine are less likely to have a response (of total symptoms or negative symptoms) than are those without AUD. Lastly, however, our data also suggest while patients with SUD are less likely to complete a 12-week haloperidol trial than those patients without SUD, for patients treated with olanzapine, the likelihood of trial completion is similar for both groups.

One limitation in this study that must be acknowledged is the lack of biological data confirming the

historical diagnoses of SUD and the lack of information regarding substance use over the course of the trial. While the rate of substance use disorder with evidence of current use at baseline was low (as compared to the rate of a lifetime history of substance use disorder), the possible differential impact of the two medications studied on substance use over the course of the trial cannot be assessed.

3.1. Comment

This international study suggests that substance use disorders are quite common in patients with first-episode schizophrenia-related psychosis. These patients have more positive symptoms at baseline, are less compliant with treatment and have a generally poorer response to treatment over a period of 12 weeks than those without SUD. These data are consistent with those of other investigators suggesting that first-episode patients with comorbid SUD may have a poor outcome (Drake and Mueser, 2001; Salyers and Mueser, 2001; Test et al., 1989; Alterman et al., 1982; Hurlburt et al., 1996; Dixon et al., 1990; Soni and Sobell, 1991; Peralta and Cuesta, 1992; DeQuardo et al., 1994; Treffert, 1978; Knudsen and Vilmar, 1984; Negrete et al., 1986; Linszen et al., 1994; Smith et al., 1997). Our data suggesting that SUD is associated with a longer DUP are important and suggest a possible area of emphasis for programs implementing early intervention strategies for patients with psychotic disorders.

The surprising finding that patients with an alcohol use disorder may have a poorer response to olanzapine (but not haloperidol) than those without an alcohol use disorder needs to be further evaluated. It will be important to assess the longer-term data from this study to determine whether the overall poorer response of the AUD patients to olanzapine at 12 weeks persists (and possibly widens) over the course of the 2-year study. By contrast, our data suggesting that dropout rate is negatively affected by SUD in patients treated with haloperidol, but not olanzapine, are of potential importance for treatment of first-episode patients, in whom maintenance on therapy is paramount.

Our data suggest that our ability to treat first-episode patients with a lifetime history of substance use disorder with antipsychotic medication, typical or atypical,

may not be as good as it is for patients without such a lifetime history. In this regard, it is important to note that relatively few of these patients had a current use disorder at recruitment, and that a lifetime history itself appears to translate into poor outcome. Given the generally poor outcome of these patients, new strategies must be developed to treat these first-episode patients. Further, since continued or new substance use will further worsen outcome in these patients (Linszen et al., 1994; Grech et al., 1999; Rolfe et al., 1999), attempts to limit such continued substance use, and prevent relapse into substance abuse for those not currently using, would appear to be essential.

A particular comment about cannabis use disorder in these first-episode patients appears in order. It was the most common substance use disorder in this population of first-episode patients with schizophrenia. (Interestingly, cannabis use disorder is also common in patients with new onset mania (Strakowski et al., 2000)). Those with a history of CUD had an earlier age of onset than those without such a history. Others have suggested that cannabis use may trigger psychosis in vulnerable individuals (Addington, 1999) and it may be particularly problematic for patients in this phase of schizophrenia. Linszen et al. (1994) reported that cessation of cannabis use after the first episode appeared to be associated with an improved outcome. Our data, and those of Linszen et al. (1994), would suggest that intervention programs directly targeting this form of substance use would be important to implement in this population.

Acknowledgements

This work was supported in part by USPHS grants MH49891, MH52373, AA49104, DA13196 (Dr. Green), grants MH00537, MH33127 (Dr. Lieberman) and Lilly Research Laboratories.

References

- Addington, J., 1999. Early intervention strategies for co-morbid cannabis use and psychosis. Proceedings of the Inaugural International Cannabis and Psychosis Conference; Melbourne, Turing the Tide Drug Strategy, State government of Victoria, pp. 15–24.
- Allebeck, P., Varla, A., Kristjansson, E., Wistedt, B., 1987. Risk factors for suicide among patients with schizophrenia. *Acta Psychiatrica Scandinavica* 76, 414–419.
- Alterman, A.I., Erdlen, D.L., Laporte, D.J., Erdlen, F.R., 1982. Effects of illicit drug use in an inpatient psychiatric population. *Addictive Behaviors* 7, 231–242.
- Birchwood, M., Todd, P., Jackson, C., 1998. Early intervention in psychosis: the critical period hypothesis. *British Journal of Psychiatry* 172, 53–59.
- Bowers, M.B., Mazure, C.M., Nelson, J.C., Jatlow, P.I., 1990. Psychotogenic drug use and neuroleptic response. *Schizophrenia Bulletin* 16, 81–85.
- Brewer, W., van Ammers, E., Francey, S., et al., 1999. Cannabis use in never medicated high-risk and first episode psychosis patients: relationship to cognition. Proceedings of the Inaugural International Cannabis and Psychosis Conference, Melbourne: Turing the Tide Drug Strategy, State government of Victoria, pp. 15–24.
- Buhler, B., Hambrecht, M., Loffler, W., an der Heiden, W., Mafner, H., 2002. Precipitation and determination of the onset and course of schizophrenia by substance abuse—a retrospective and prospective study of 232 population-based first illness episodes. *Schizophr. Res.* 54, 243–250.
- Cantwell, R., Brewin, J., Glazebrook, C., et al., 1999. Prevalence of substance misuse in first-episode psychosis. *British Journal of Social Psychiatry* 174, 150–153.
- Curry, C., Smith, D., McGorry, P., 1999. The intensity, prevalence, and client characteristics of cannabis use in first onset psychosis. Paper Presented at the Inaugural International Cannabis and Psychosis Conference; Melbourne, Australia.
- DeQuardo, J.R., Carpenter, C.F., Tandon, R., 1994. Patterns of substance abuse in schizophrenia: nature and significance. *Journal of Psychiatric Research* 28, 267–275.
- Dixon, L., Haas, G., Weiden, P., Sweeney, J., Frances, A., 1990. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self reports. *Schizophrenia Bulletin* 16, 69–79.
- Drake, R.E., Brunette, M.F., 1998. Complications of severe mental illness related to alcohol and drug use disorders. In: Galanter, M. (Ed.), *Recent Developments in Alcoholism*. Plenum, New York, pp. 285–299.
- Drake, R.E., Mueser, K.T., 2001. Substance abuse comorbidity. In: Lieberman, J.A., Murray, R.M. (Eds.), *Comprehensive Care of Schizophrenia*. Martin Dunitz, London, pp. 243–254.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. *Structured Clinical Interview for DSM IV-Axis I Disorders*. APA Press, Washington, DC.
- Grech, A., Van Os, J., Murray, R.M., 1999. Influence of cannabis on the outcome of psychosis. *Schizophrenia Research* 36, 41.
- Green, A.I., Zimmet, S.V., Strous, R.D., Schildkraut, J.J., 1999. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? *Harvard Review of Psychiatry* 6, 287–296.
- Green, A.I., Salomon, M.S., Brenner, M.J., Rawlins, K., 2002. Treatment of schizophrenia and comorbid substance use disorder. *Current Drug Targets. CNS & Neurological Disorders* 1, 129–139.

- Gut-Fayand, A., Dervaux, A., Olie, J.P., Loo, H., Poirier, M.F., Krebs, M.O., 2001. Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity. *Psychiatry Research* 102, 65–72.
- Haas, G.L., Garratt, L.S., Sweeney, J.A., 1998. Delay to first antipsychotic medication in schizophrenia: impact on symptomatology and clinical course of illness. *Journal of Psychiatric Research* 32, 151–160.
- Hambrecht, M., Hafner, H., 1996. Substance abuse and the onset of schizophrenia. *Biological Psychiatry* 40, 1155–1163.
- Harkavy-Friedman, J.M., Nelson, E., 1997. Management of the suicidal patient with schizophrenia. *Psychiatric Clinics of North America* 20, 625–640.
- Ho, B., Andreasen, N.C., Flaum, M., Nopoulos, P., Miller, D., 2000. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *American Journal of Psychiatry* 157, 808–815.
- Hurlburt, M.S., Hough, R.L., Wood, P.A., 1996. Effects of substance abuse on housing stability of homeless mentally ill persons in supported housing. *Psychiatric Services* 47, 731–736.
- Khantzian, E.J., 1985. A self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *American Journal of Psychiatry* 142, 1259–1264.
- Khantzian, E.J., 1997. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harvard Review of Psychiatry* 4, 231–244.
- Knudsen, P., Vilmar, T., 1984. Cannabis and neuroleptic agents in schizophrenia. *Acta Psychiatrica Scandinavica* 69, 162–174.
- Kovaszny, B., Fleischer, J., Tanenberg-Karant, M., Jandorf, L., Miller, A.D., Bromet, E., 1997. Substance use disorder and the early course of illness in schizophrenia and affective psychosis. *Schizophrenia Bulletin* 23, 195–201.
- Lammertink, M., Lohrer, F., Kaiser, R., Hambrecht, M., Pukrop, R., 2001. Differences in substance abuse patterns: multiple drug abuse alone versus schizophrenias with multiple drug abuse. *Acta Psychiatrica Scandinavica* 104, 361–366.
- Lieberman, J., Tohen, M., Green, A., et al., 2003. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized double-blind trial of olanzapine vs. haloperidol. *American Journal of Psychiatry* 160, 1396–1404.
- Lindelius, R., Kay, D., 1973. Some changes in the pattern of mortality in schizophrenia in Sweden. *Acta Psychiatrica Scandinavica* 49, 315–323.
- Linszen, D.H., Dingemans, P.M., Lenior, M.E., 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* 51, 273–279.
- Loebel, A.D., Lieberman, J.A., Alvir, J.M.J., Mayerhoff, D.L., Geisler, S.H., Szymanski, S.R., 1992. Duration of psychosis and outcome in first-episode schizophrenia. *American Journal of Psychiatry* 149, 1183–1188.
- McGlashen, T.H., Fenton, W.S., 1993. Subtype progression and pathopsychologic deterioration in early schizophrenia. *Schizophrenia Bulletin* 19, 71–84.
- Moscarelli, M., Capri, S., Neri, L., 1991. Cost evaluation of chronic schizophrenic patients during the first 3 years after the first contact. *Schizophrenia Bulletin* 17, 421–426.
- Mueser, K.T., Yarnold, P.R., Levinson, D.F., et al., 1990. Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. *Schizophrenia Bulletin* 16, 31–56.
- Mueser, K.T., Bennett, M., Kushner, M.G., 1995. Epidemiology of substance use disorders among persons with chronic mental illness. In: Lehman, A.F., Dixon, L.B. (Eds.), *Double Jeopardy: Chronic Mental Illness and Substance Use Disorders*. Harwood Academic Publishers, Netherlands, pp. 9–25.
- Negrete, J.C., Knapp, W.P., Douglas, D.E., Smith, W.B., 1986. Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. *Psychological Medicine* 16, 515–520.
- Olney, J.W., Farber, N.B., 1995. Glutamate receptor dysfunction and schizophrenia. *Archives of General Psychiatry* 52, 998–1007.
- Osher, F.C., Kofoed, L.L., 1989. Treatment of patients with both psychiatric and psychoactive substance use disorders. *Hospital and Community Psychiatry* 40, 1025–1030.
- Peralta, V., Cuesta, M.J., 1992. Influence of cannabis abuse on schizophrenic psychopathology. *Acta Psychiatrica Scandinavica* 85, 127–130.
- Rolfé, T.J., McGory, P., Cooks, J., Longley, T., Plowright, D., 1999. Cannabis use in first episode psychosis: incidence and short-term outcome. *Schizophrenia Research* 36, 313.
- Roy, A., Mazonson, A., Pickar, D., 1984. Attempted suicide in chronic schizophrenia. *British Journal of Psychiatry* 144, 303–306.
- Salyers, M.P., Mueser, K.T., 2001. Social functioning, psychopathology, and medication side effects in relation to substance use and abuse in schizophrenia. *Schizophrenia Research* 48, 109–123.
- Sheitman, B.B., Lieberman, J.A., 1998. The natural history and pathophysiology of treatment resistant schizophrenia. *Journal of Psychiatric Research* 32, 143–150.
- Siris, S.G., 1990. Pharmacological treatment of substance-abusing schizophrenic patients. *Schizophrenia Bulletin* 16, 111–122.
- Smith, C.M., Barzman, D., Pristach, C.A., 1997. Effect of patient and family insight on compliance of schizophrenic patients. *Journal of Clinical Pharmacology* 37, 147–154.
- Soni, S., Sobell, M., 1991. Alcohol abuse in chronic schizophrenics: implications for management in the community. *Acta Psychiatrica Scandinavica* 84, 272–276.
- Soyka, M., Albus, M., Kathmann, N., et al., 1993. Prevalence of alcohol and drug abuse in schizophrenic inpatients. *European Archives of Psychiatry and Clinical Neuroscience* 242, 362–372.
- Strakowski, S.M., DelBello, M.P., Fleck, D.E., Arndt, S., 2000. The impact of substance abuse on the course of bipolar disorder. *Biological Psychiatry* 48, 477–485.
- Test, M.A., Wallisch, L.S., Allness, D.J., Ripp, K., 1989. Substance abuse in young adults with schizophrenic illness. *Schizophrenia Bulletin* 15, 465–475.
- Treffert, D.A., 1978. Marijuana use in schizophrenia: a clear hazard. *American Journal of Psychiatry* 135, 1213–1215.
- Tsuang, M.T., 1978. Suicide in schizophrenics, manics, depressives, and surgical controls: a comparison with general population suicide mortality. *Archives of General Psychiatry* 35, 153–155.
- Tsuang, M.T., Fleming, J.A., Simpson, J.C., 1999. Suicide and

- schizophrenia. In: Jacobs, D.G. (Ed.), *The Harvard Medical School Guide to Suicide Assessment and Intervention*. Jossey-Bass, San Francisco, pp. 287–299.
- Verdoux, H., Liraud, F., Gonzales, B., Assens, F., Abalon, F., van Os, J., 1999. Suicidality and substance misuse in first-admitted subjects with psychotic disorder. *Acta Psychiatrica Scandinavica* 100 (5), 389–395.
- Waddington, J.L., Buckley, P.F., Scully, P.J., Lane, A., O'Callaghan, E., Larkin, C., 1998. Course of psychopathology, cognition and neurobiological abnormality in schizophrenia: developmental origins and amelioration by antipsychotics? *Journal of Psychiatric Research* 32, 179–189.
- Wilkinson, D.G., 1982. The suicide rate in schizophrenia. *British Journal of Psychiatry* 140, 138–141.
- Wyatt, R.J., 1991. Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin* 17, 325–351.