Comorbid substance use and age at onset of schizophrenia

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Background Substance use may be a risk factor for the onset of schizophrenia.

Aims To examine the association between substance use and age at onset in a UK, inner-city sample of people with recent-onset schizophrenia.

Method The study sample consisted of 152 people recruited to the West London First-Episode Schizophrenia Study. Self-reported data on drug and alcohol use, as well as information on age at onset of psychosis, were collected. Mental state, cognition (IQ, memory and executive function) and social function were also assessed.

Results In total, 60% of the participants were smokers, 27% reported a history of problems with alcohol use, 35% reported current substance use (not including alcohol), and 68% reported lifetime substance use (cannabis and psychostimulants were most commonly used). Cannabis use and gender had independent effects on age at onset of psychosis, after adjusting for alcohol misuse and use of other drugs.

Conclusions The strong association between self-reported cannabis use and earlier onset of psychosis provides further evidence that schizophrenia may be precipitated by cannabis use and/or that the early onset of symptoms is a risk factor for cannabis use.

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Substance use in people with schizophrenia is more common than in the general population, and is associated with poor clinical and social outcomes (Blanchard *et al*, 2000; Kavanagh *et al*, 2002). Substance use may also be a risk factor for the onset of the disorder (Smit *et al*, 2004; Semple *et al*, 2005), and the use of cannabis in adolescence has been reported to increase the risk of developing symptoms of schizophrenia in adulthood (Tsapakis *et al*, 2003). One piece of supportive evidence is that some first-episode studies have found an earlier age at onset for individuals with a history of comorbid substance use (Rabinowitz *et al*, 1998; Mastrigt *et al*, 2004; Veen *et al*, 2004), although not all studies have shown this (Cantor-Graee *et al*, 2001; Sevy *et al*, 2001). The present study was designed to assess the influence of substance use on the age at onset of psychosis in first-episode schizophrenia in West London, and to examine the relationship between a history of comorbid substance use and measures of the nature and severity of symptoms, and social and neuropsychological function.

METHOD

Participants

Individuals were recruited as part of a prospective longitudinal study of first-episode schizophrenia in West London. Details of the study design and entry criteria can be found elsewhere (Hutton *et al*, 1998), as can information on symptom severity, adherence to treatment, duration of untreated psychosis (DUP) and cognitive function in samples derived from this study (Barnes *et al*, 2000; Joyce *et al*, 2002; Mutsatsa *et al*, 2003). The patients who were eligible for inclusion in this study were aged between 16 and 50 years, had received no more than 12 weeks of antipsychotic medication, and in most cases were seen at the time of their first admission to hospital. For each patient, a diagnosis of DSM–IV (American Psychiatric Association, 1994) schizophrenia or schizophreniform disorder was confirmed at diagnostic review by two senior clinicians (E.M.J. and T.R.E.B.).

Assessments

Basic demographic data were collected from the patients and their case notes. Lifetime alcohol and substance use were recorded using the Substance Use Rating Scale, patient version (SURSp; Duke *et al*, 1994). This scale allows the identification of patients with drinking problems, and elicits any evidence of alcohol dependency, as well as collecting information on the nature of current drug use (within the past month) and previous drug use.

Information relating to the date of onset of psychotic symptoms was elicited using a modified questionnaire (Loebel *et al*, 1992; Barnes *et al*, 2000). Relevant information was also collected from the clinical case notes, and by questioning the patient and their relatives and/or carers. Any discrepancy between the different sources was discussed within the research team, and the information that was deemed to be most reliable was used. The DUP, namely the time from onset of psychotic symptoms to first treatment with antipsychotic medication, was calculated for each patient.

Global severity of illness was assessed using the Clinical Global Impression Scale (CGI; Guy, 1976). Mental state was assessed using the Scale for Assessment of Positive Symptoms and the Scale for Assessment of Negative Symptoms (SAPS and SANS respectively; Andreasen, 1990). Scores for three symptom-derived syndromes of schizophrenia were calculated for each patient by adding together the global sub-scale scores pertaining to each factor, and dividing by the maximum possible score to give a value between 0 and 1 for each factor. The syndromes were categorised as follows: positive syndrome (SAPS hallucinations and delusions); disorganisation syndrome (SAPS bizarre behaviour and positive formal thought disorder); and negative syndrome (all SANS sub-scales). The Comprehensive Psychopathological Rating Scale (CPRS; Åsberg *et al*, 1978) was also administered, from which a score for the 10-item Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) was calculated.

Social function was assessed using the Social Function Scale (SFS; Birchwood *et al*, 1990), which asks individuals to rate their abilities in seven areas of social function, namely activation–engagement, interpersonal communication, frequency and competence with regard to activities of daily living, participation in social activities, participation in recreational activities, and employment or occupational activity. The Rating of Medication Influences (ROMI; Weiden *et al*, 1994) was used to assess positive and negative attitudes towards medication.

Premorbid IQ was estimated using the National Adult Reading Test (NART, revised version; Nelson, 1991), and current, full-scale IQ was assessed using a short form of the Wechsler Adult Intelligence Scale – Revised (WAIS–R; Missar *et al*, 1994) with four sub-tests. The main measures of neurocognitive function were the memory and executive function tests from the computerised Cambridge Automated Neuropsychological Test Battery (CANTAB; Sahakian & Owen, 1992), run on an IBM-compatible PC with a touch-sensitive screen. The memory tests assessed spatial span and pattern recognition memory, and executive function was assessed by means of a planning task (a modified version of the Tower of London test; Shallice, 1982) and a test of spatial working memory. We have described these tests, the performance measures used and the derivation of the test scores in our patients elsewhere (Hutton *et al*, 1998).

Data analysis

The data were analysed using the Statistical Package for the Social Sciences, version 12 for Windows. In a comparison of patients with and without a history of substance use, the *t*-test was employed for continuous data and the χ^2 test was used for categorical data. Age at onset of psychosis was used as the outcome variable in a linear regression model, and potentially influential variables (relating to gender and substance use) were entered as independent variables.

RESULTS

Information on lifetime substance use was collected at interview for 152 patients (110 men and 42 women) with DSM–IV schizophrenia or schizophreniform disorder, who were studied at the time of their first presentation to psychiatric services,

Table I Clinical characteristics of patients with and without a lifetime history of substance use

Variable	No lifetime history of substance use (n=42)	Any lifetime history of substance use (n=110)	Test statistic		P
			t	χ^2	
Male/female ratio, n	26/16	84/26		3.17	0.075
Age at first psychiatric contact, years: mean (s.d.)	27.8 (10.4)	24.4 (6.1)	2.54		0.012
Age at onset of psychosis, years: mean (s.d.)	26.1 (9.2)	23.3 (5.9)	2.14		0.033
Duration of untreated psychosis, weeks: mean (s.d.)	51.9 (83.7)	56.4 (83.1)	−0.29		0.77
Employed (or student), %	41	37		0.29	0.59

but the data were incomplete in 6 cases. On the basis of these data, which were obtained using the SURSp, the sample was divided into two subgroups, namely those reporting a history of alcohol misuse (problem drinking, with or without evidence of dependent drinking) and/or substance use (*n*=110), and those with no such history (*n*=42). In the former group, most patients described both alcohol misuse and substance use, and only 5 patients reported current or lifetime problem drinking or evidence of dependent drinking in the absence of any other substance use. The clinical characteristics of the two subgroups are listed in Table 1. Further sub-categorisation of the sample on the basis of the reported profile of substances used was not possible because of the overlap in substances used. For example, 90% of the patients with a history of any type of substance use reported the use of cannabis.

For the total sample, the median DUP was 24 weeks. The mean DUP did not differ significantly between those with and without substance use (see Table 1). However, the patients with a reported lifetime history of substance use were significantly younger at the time of the assessment (*t*=2.45, d.f.=148, *P*=0.012), and were also significantly younger at the onset of their psychotic symptoms (*t*=2.15, d.f.=148, *P*=0.033). Linear regression analysis was performed with age at onset as the outcome variable and with the following four independent variables: gender; any report of alcohol misuse (problem or dependent drinking); any report of cannabis use; and any report of substance

use other than cannabis use. Alcohol misuse and any substance use (other than cannabis use) were not significant in relation to age at onset (estimated mean age 1.6 years older in patients reporting alcohol misuse, 95% CI −1.1 to 4.2, *P*=0.2; estimated mean age 1.9 years older in users of drugs other than cannabis, 95% CI −0.9 to 4.9, *P*=0.2). However, gender and cannabis use were found to be significant. The results indicate that in this sample the age at onset of psychosis was on average 4.2 years older for women (95% CI 1.7–6.8, *P*=0.001) when adjusted for substance use. Cannabis use was significantly associated with a younger onset by a mean value of 5 years (95% CI 1.9–8.1, *P*=0.002), adjusted for gender and substance use other than cannabis use. This means that those patients in the sample who reported that they had used cannabis had an earlier age at onset of psychosis than other patients who did not report cannabis use but who shared the same profile with regard to the other variables (e.g. comparing men who reported alcohol misuse and use of both cannabis and other drugs with men who had the same characteristics apart from the fact that they had not used cannabis).

We have reported elsewhere (Joyce *et al*, 2005) that premorbid IQ (measured by the NART) was associated with earlier onset of psychosis in a sample that was also derived from the West London First-Episode Schizophrenia Study. The NART score was entered as an additional independent variable in the present linear regression analysis, and it was found to be significant, whereas cannabis use remained significant (an estimated increase of 0.24

years in age at onset per unit increase in NART; 95% CI 0.12–0.37, $P < 0.0002$).

Data on the nature and prevalence of alcohol and drug use in those participants who provided a full report are shown in Table 2. Cannabis was the substance most commonly used. In total, 94 patients in the sample had used this drug at some time, of whom only 25 patients (27%) had not used other drugs. The other drugs that had been used, in descending order of reported use, were amphetamines and stimulants (including cocaine), ecstasy, lysergic acid diethylamide (LSD), opiates (including heroin), barbiturates and benzodiazepines, other substances (e.g. khat) and phencyclidine (PCP). With regard to alcohol misuse, 40 patients reported a history of problem drinking, of whom 29 patients (72.5%) fulfilled the criteria for dependent drinking.

In Table 3, data for the two patient subgroups are compared with regard to the clinical and neuropsychological assessments that were administered. The patients who were substance users had a

Table 2 Nature and frequency of alcohol and substance use in the total sample ($n = 148$) and in the subsample of patients who reported lifetime alcohol and/or substance use ($n = 106$)

	Total sample (%)	Subsample alcohol and/ or substance use (%)
Smoker	60.1	68.9
Alcohol use		
Problem drinking	27.0	37.8
+evidence of dependence	19.6	27.4
Substance use		
In previous month	34.7	48.6
Lifetime	68.2	95.3
Lifetime use of drugs[1]		
Cannabis	64.4	90.4
Stimulants[2]	37.7	52.9
Ecstasy	32.9	46.1
Hallucinogens	30.8	43.3
Opiates/heroin	11.6	16.3
Barbiturates/ benzodiazepines	8.9	12.5
Other (including khat)	5.4	7.7
PCP (angel dust)	4.8	6.7

PCP, phencyclidine.
1. Data for two patients missing from each group.
2. Amphetamines and cocaine.

Table 3 Mental state and neuropsychological assessment variables for patients with and without a lifetime history of substance use

Variable	No lifetime history of substance use	Any lifetime history of substance use	t	P
n	42	110		
Symptom-based syndrome scores				
Negative symptoms: mean (s.d.)	0.42 (0.29)	0.42 (0.25)	−0.03	0.98
Hallucinations and delusions: mean (s.d.)	0.60 (0.32)	0.73 (0.41)	−1.85	0.066
Disorganisation: mean (s.d.)	0.39 (0.31)	0.43 (0.29)	−0.88	0.38
CGI severity score: mean (s.d.)	4.18 (1.3)	4.82 (1.1)	−2.99	0.003
MADRS score: mean (s.d.)	17.1 (9.6)	18.1 (10.1)	−0.54	0.59
Social Function Scale score: mean (s.d.)	113.1 (12.9)	111.7 (10.2)	0.63	0.53
ROMI score				
Positive score: mean (s.d.)	12.2 (3.7)	12.9 (4.9)	−0.67	0.51
Negative score: mean (s.d.)	14.3 (5.4)	16.1 (6.2)	−1.32	0.19
Neuropsychological tests				
NART				
n	29	73		
mean (s.d.)	99.5 (9.6)	99.5 (10.6)	−0.01	0.99
Full-scale IQ: WAIS–R				
n	30	73		
mean (s.d.)	91.9 (13.1)	92.8 (15.5)	−0.29	0.77
Spatial span score				
n	35	84		
mean (s.d.)	5.6 (1.7)	5.5 (1.3)	0.54	0.59
Pattern recognition memory: number correct (maximum=24)	36	81		
n	20.1 (2.9)	20.2 (3.1)	−0.76	0.94
mean (s.d.)				
Spatial working memory: total number of errors	34	85		
n	37.9 (21.7)	32.0 (20.7)	1.38	0.17
mean (s.d.)	34	83		
Planning: number of perfect solutions (maximum=12)	7.7 (2.3)	7.3 (2.0)	1.01	0.34
n				
mean (s.d.)				

CGI, Clinical Global Impression; MADRS, Montgomery–Åsberg Depression Rating Scale; ROMI, Rating of Medication Influences; NART, National Adult Reading Test; WAIS–R, Wechsler Adult Intelligence Scale – Revised.

significantly higher mean CGI score ($t = -2.99$, d.f.=138, $P = 0.003$) and there was a trend towards a higher mean score on the positive symptoms syndrome (hallucinations and delusions) ($t = -1.85$, d.f.=150, $P = 0.066$). There was also a trend towards an association of substance use with male gender ($\chi^2 = 3.18$, d.f.=1, $P = 0.075$). There were no statistically significant differences between the two groups with regard to mean SFS total score, mean ROMI positive and negative scores or mean MADRS total score. Neuropsychological test results were only obtained for a subsample of the patients (see Table 3). Analysis of the data revealed no significant differences between substance users and non-users on performance measures for any of the neuropsychological tasks.

DISCUSSION

Earlier age at onset

We found an earlier age at onset of psychosis in patients who reported a lifetime history of comorbid substance use. One

explanation for this is that the illness is precipitated by substance use, although it remains uncertain whether this effect is limited to people with a predisposition to psychosis (Smit *et al*, 2004; Henquet *et al*, 2005). Another possible explanation is that the early onset of symptoms is a risk factor for substance use. The experience of symptoms could make patients vulnerable to substance use, perhaps in an attempt to cope with the illness or to self-medicate (Hambrecht & Häfner, 1996; Addington & Addington, 1998; Degenhardt *et al*, 2003). These hypotheses have been explored in previous studies by examining the temporal relationship between the onset of schizophrenia and substance use. The findings have been inconsistent (Hambrecht & Häfner, 1996, 2000), and have generally only addressed the relationship between substance use and the onset of psychotic symptoms, and not the possible relevance of prodromal symptoms. Furthermore, the relatively high proportion of patients who reported lifetime substance use in this and other first-episode studies raises the possibility that substance-related symptoms could confound retrospective estimation of DUP and age at onset. For example, drug-induced phenomena may be mistaken for early symptoms of illness or substance use may mask psychotic symptoms (Larsen *et al*, 2001). In the latter situation, if patients perceive their early psychotic symptoms to be drug-induced, this may delay their seeking help for illness and thus prolong the DUP. Norman & Malla (2002) proposed more generally that substance use by people with psychosis may partly reflect denial of the severity of their illness and of the potential benefit of medical intervention, and may thus be associated with a reduced likelihood of seeking treatment soon after the onset of psychosis. However, our findings do not support such a view, insofar as we found no relationship between a history of substance use and DUP.

Our data do not allow us to determine whether or not the use of drugs preceded the onset of psychotic and/or prodromal symptoms in the majority of patients. Furthermore, the marked overlap between patients who were using alcohol, cannabis and other drugs limits analysis of the influence of a particular substance. However, the results of the linear regression analysis suggest that cannabis use is more strongly associated with earlier onset of psychosis than either alcohol misuse or other drug use. This finding is consistent with the results of other studies (Smit *et al*, 2004; Veen *et al*, 2004) and it supports the view that cannabis use is a risk factor for the onset of psychosis.

Prevalence and nature of substance use in first-episode schizophrenia

The results of this study confirm the high rates of substance use reported previously (particularly for nicotine, alcohol and cannabis) in individuals presenting to psychiatric services with their first episode of schizophrenia (Hambrecht & Häfner, 1996; Mastrigt *et al*, 2004). Both the prevalence and the profile of substances used by the participants in our sample are similar to those reported in previous out-patient and community studies of schizophrenia in the UK (e.g. Duke *et al*, 1994, 2001; Condren *et al*, 2001), with nicotine, alcohol and cannabis being most commonly used, but stimulants and hallucinogens also being popular. When considering the extent to which our findings can be generalised, it might be argued that the prevalence figures for comorbid substance use in patients with schizophrenia in London tend to be higher than those in many other parts of the UK (Weaver *et al*, 2003).

The high prevalence of tobacco smoking that was found in our study is consistent with evidence that this habit is particularly strongly associated with schizophrenia compared with other forms of severe mental illness, and that smoking-related diseases are more common in people with schizophrenia than in the general population (DeLeon *et al*, 2002). The reasons why people with schizophrenia tend to be heavy smokers remain uncertain, but possible explanations relate to a therapeutic effect of nicotine on psychotic symptoms and/or the neurocognitive deficits associated with the disorder, or to an increase in the metabolism of antipsychotic drugs with smoking, causing a reduction in the side-effect burden (Jeste *et al*, 1996). The latter explanation would not appear to be relevant to the patients in our sample, as they were already smoking when they first presented to psychiatric services, which suggests that there is a relationship with the psychotic illness rather than with the medication.

Assessment of substance use by self-report

Self-reported data on substance use can provide a reliable and valid basis for prevalence estimation (Weaver *et al*, 2003), and such an assessment method has the potential to gather information on past use. For example, the self-report time-line follow-back procedure (Sobell *et al*, 2001) for evaluating retrospective self-reported estimates of daily alcohol consumption can be reliably used by clinicians and researchers to collect information on drinking habits up to 12 months before the interview. A limitation of the present study is that our enquiries about past substance use did not include detailed assessment of the frequency and amounts of illicit drugs taken, as well as dependency. It remains uncertain whether precise information on the frequency, intensity and timing of use of the full range of substances reported, sometimes over periods of several years, could have been reliably gathered retrospectively. The lack of such data means that some of the patients with a history of lifetime substance use who were identified in this study may have been infrequent users. However, the evidence suggests that even relatively low levels of comorbid substance use are associated with a poorer outcome in schizophrenia, including a greater risk of relapse and a poorer response to conventional antipsychotic medication (Drake & Brunette, 1998; Kavanagh *et al*, 2004), and this seems to hold true for first-episode patients, even in the short term (Caspari, 1999; Sorbara *et al*, 2003).

Symptom and cognitive correlates of comorbid substance use

The finding of a significantly higher mean CGI score in those using substances is consistent with numerous previous reports of more severe illness in people with schizophrenia and comorbid substance use (Brunette *et al*, 1997). However, there was no significant association with positive psychotic symptoms, which may partly reflect the fact that positive symptoms would have been present in virtually all of the patients in the sample, as the mental state assessments were usually conducted during the first admission to hospital with overt psychosis. Our findings do not suggest that substance use has an effect on the presentation of other symptoms. An association between comorbid substance use and less severe negative symptoms has been reported in several previous studies of patients with schizophrenia (Brunette *et al*, 1997), but has not consistently emerged

in first-episode studies (Linszen *et al*, 1994; Hambrecht & Häfner, 1996; Sevy *et al*, 2001). We did not find such an association in the present study. Similarly, we found no relationship between substance use and depressive features. Several previous studies of patients with established schizophrenia have more commonly found depressive symptoms in individuals with comorbid substance use, but such an association has not been a feature of studies of first-episode psychosis (Linszen *et al*, 1994; Sevy *et al*, 2001).

Previous findings that substance use was associated with significantly better premorbid cognitive functioning and higher current full-scale IQ prompted the theory that first-episode patients who have used substances may have been better able to obtain them because they had more opportunity, greater resources and possibly better social skills (Salyers & Mueser, 2001; Sevy *et al*, 2001). This hypothesis is not supported by the findings of our study. Comparison of patients with and without comorbid substance use revealed no significant differences with regard to premorbid IQ (as estimated by the NART), current full-scale IQ or performance on the tests of memory and executive function. Furthermore, the two groups were rated as having similar levels of social function. Our data are consistent with those of Pencer & Addington (2003), who also found no association between mild-to-moderate substance misuse and cognitive impairment in patients with first-episode psychosis. They suggested that any deleterious or specific effect of substance use on cognition in people with schizophrenia occurs only after prolonged use. We have previously found that a lower premorbid IQ is associated with an earlier age at onset (Joyce *et al*, 2005). In the current patient sample, a regression analysis revealed that premorbid IQ and substance misuse were independent predictors of earlier age at onset.

Adherence to treatment

In patients with established schizophrenia, comorbid substance use has been shown to be a major determinant of adherence to treatment (Olfson *et al*, 2000). The poorer prognosis, particularly the higher relapse rate, in people with schizophrenia who use substances may be partly explained by reduced adherence to the medication regimen. However, in the sample of patients that we studied, we found no relationship between attitudes to medication that are relevant to adherence (as assessed by the ROMI) and substance use. These findings suggest that, among people with schizophrenia, a history of substance use at the time of first presentation to psychiatric services does not reliably identify those individuals who already have negative attitudes to medication and treatment.

Clinical implications

These results confirm the high prevalence of lifetime substance use in first-episode patients with schizophrenia. Although alcohol and cannabis were the substances most commonly used, most patients reported a history of multiple substance use. From a clinical perspective, given that such substance use tends to predict a poorer initial outcome, our findings reinforce the need to routinely assess and consider appropriate intervention for substance use in people with schizophrenia when they first present to pyschiatric services.

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CLINICAL IMPLICATIONS

■ Systematic assessment of substance use is warranted in patients with recent-onset schizophrenia.

■ The use of cannabis and other substances by psychologically vulnerable adolescents should be discouraged.

■ Retrospective assessment of the duration of untreated psychosis should take account of the possible confounding effect of symptoms related to substance use.

LIMITATIONS

■ The study population consisted of an urban sample of patients in the UK, and this limits the extent to which the findings can be generalised.

■ The assessment of substance use did not include frequency of use or dependence.

■ The assessors who recorded the reports of substance use were not masked to the mental state of the patients.

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