SHORT REPORT

Increased extrapyramidal symptoms in patients with schizophrenia and a comorbid substance use disorder

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Few data have been gathered about the impact of psychoactive substances on extrapyramidal symptoms (EPS) in schizophrenia, and so far, inconsistent results have been reported. We studied 41 outpatients with schizophrenia (based on DSM-IV criteria), who were divided into two groups: with (n = 17) and without (n = 24) a substance use disorder (alcohol, cannabis, and/or cocaine). Both groups were matched for sociodemographic data and psychiatric symptoms (Positive and Negative Syndrome Scale). EPS were evaluated with the Extrapyramidal Symptoms Rating Scale and the Barnes Akathisia Scale, and all patients were stable on either quetiapine or clozapine. Patients receiving anticholinergic drugs were excluded. Analyses of variance were conducted on both groups and showed that schizophrenia patients with a comorbid substance use disorder (especially cocaine) displayed more EPS compared with non-abusing patients.

The lifetime prevalence of substance use disorders (SUD) in schizophrenia is close to 50%. In decreasing order, patients misuse alcohol, cannabis, and cocaine. Psychoactive substances (PAS) have negative consequences on the course of the pathology, which result in a higher incidence of psychotic relapses, depressive episodes, homelessness, unemployment, and legal and health problems.[1]

Antipsychotic medications have been the mainstay of schizophrenia treatment since the early 1950s. Efficacious for positive symptoms, antipsychotic treatment can lead to disabling extrapyramidal symptoms (EPS), such as parkinsonian signs, dystonia, and dyskinesia. These antipsychotic induced EPS (especially parkinsonism) are most probably related to striatal dopaminergic blockade.[2]

PAS may interact with antipsychotics in the development of EPS. Indeed, most PAS exert an impact on the basal ganglia,[3] despite heterogeneous mechanisms of action. Although not systematically studied, most PAS have been associated with extrapyramidal side effects.[4] Cocaine has been associated with signs of parkinsonism, dystonia, dyskinesia and akathisia.[5] Cocaine blocks dopamine transporters localised in the nigrostriatal system, in which the dopaminergic neurones project for the substantia nigra pars compacta to the dorsolateral striatum. In its acute effects, cocaine increases striatal dopamine release in humans.[5] However, its chronic effects are associated with striatal dopaminergic downregulation,[6] similar to the striatal dopamine deficit observed in Parkinson's disease. In the case of alcohol, the withdrawal from this PAS is associated with signs of autonomic hyperactivity, including tremors. Whether chronic alcohol consumption is a risk factor for movement disorders remains controversial. As for cannabis, its effects on movement in humans are not well documented, but animal studies show that it induces catalepsy and potentiates neuroleptic induced hypokinesia. The main psychoactive agent of cannabis (Δ^9-tetrahydrocannabinol) binds to the CB_1 cannabinoid receptor localised in the substantia nigra pars reticulata and globus pallidus. The CB_1 receptor has been shown to be involved in movement inhibition in animals.[7]

Few data have been gathered about the effects of PAS on EPS in schizophrenia and inconsistent results have been reported. Some studies have shown increased EPS,[8 9] whereas others have shown no difference,[10] or even decreased EPS in dual diagnosis patients.[11] The most consistent finding has been the increased risk for tardive dyskinesia in dual diagnosis patients.[9 12]

The study of EPS in dual diagnosis is a difficult topic, as numerous confounding factors may affect results. Noticeably, most published studies have not systematically controlled for variables such as psychiatric symptoms, antipsychotic dosage, and anticholinergic drugs. The current study sought to investigate the effects of PAS on EPS in dual diagnosis schizophrenia, while controlling for these factors.

METHODS

Participants

In total, 41 outpatients with a schizophrenia spectrum disorder diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV) participated in the study. The scientific research programme was approved by the local ethics committee and all subjects gave written informed consent.

Participants were divided into two groups: with and without a SUD (misuse/dependence in the past 3 months). A cross sectional study design produced 24 patients in the dual diagnosis (DD) group and 17 patients in the schizophrenia only (SCZ) group. Patients from the DD group suffered from one or more of the following SUD: alcohol only (n = 5), cannabis only (n = 12), and cocaine plus alcohol or cannabis (n = 7). SUD diagnoses were complemented with urinary drug screenings. Only patients who had been treated for more than a month either with clozapine or quetiapine (associated with the lowest EPS liability[13]) were included in study. Only five patients were being treated with clozapine, all in the SCZ group. The potential effects of antipsychotics on EPS were considered through dose equivalency estimation to 100 mg/day of chlorpromazine.[14] Medication adherence was verified using pill count. Patients receiving anticholinergics were excluded from the study.

Assessments

The Positive and Negative Syndrome Scale (PANSS)[15] was administered to measure severity of schizophrenia symptoms.

Abbreviations: DD, dual diagnosis; EPS, extrapyramidal symptoms in schizophrenia; ESRS, Extrapyramidal Symptoms Rating Scale; PANSS, Positive and Negative Syndrome Scale; PAS, psychoactive substances; SCID-IV, Structured Clinical Interview for DSM-IV; SCZ, schizophrenia only

EPS were evaluated with the Extrapyramidal Symptoms Rating Scale (ESRS).[16] The ESRS provides a score for the patients' subjective appraisal of his symptoms, objective scores for parkinsonism, dystonia and dyskinesia, and a global evaluation of EPS. Akathisia was evaluated with the Barnes Akathisia Scale.[17] EPS were assessed by three experienced physicians (TP, AMM, RHB), who were not blinded to drug misuse status but were blind to the objective of the study. Quantities of any PAS used in the past week by patients in the DD group were also registered. Money spent on PAS was calculated based on the value market in Quebec province, Canada.

Statistical analyses

Differences in EPS between the DD and SCZ groups were analysed using one way analyses of variance with group as the independent variable. Independent *t* tests were used to analyse potential differences in sociodemographic data and psychiatric symptoms between groups. Dichotomous variables were evaluated using Pearson's χ^2 test. Correlation analyses were performed using Pearson's test. Statistical analyses were performed using the Statistical Package for Social Sciences (version 10).

RESULTS

Both groups of patients did not differ in terms of age (mean (SD) SCZ 31.8 (10.9) years, DD 31.4 (10.5) years; $t = 0.096$; $p = 0.924$), sex (SCZ 5 women and 12 men, DD 3 women and 21 men; $\chi^2 = 1.812$; $p = 0.178$), ethnicity (SCZ 15/17 white, DD 23/24 white), educational level (SCZ 11.9 (2.5) years, DD11.1 (2.1) years; $t = 0.994$; $p = 0.329$), or duration of illness (SCZ 107.4 (103.8) months, DD 101.6 (105.3) months; $t = 0.176$; $p = 0.861$). No differences emerged between the two groups for antipsychotic dosage (SCZ 870.7 (347.7) mg, DD 761.2 (327.8) mg; $t = 1.018$; $p = 0.316$). There were also no differences between the two groups in psychiatric symptoms, assessed with the PANSS (total score SCZ 86.5 (15.5), DD80.2 (10.3); $t = 1.477$; $p = 0.152$). Affective symptoms were controlled for using the PANSS item ''affective factor'' (for example, somatic concern, anxiety, guilt, tension, and depression items). Again, no differences were noticed between the two groups (SCZ 12.8 (2.7), DD 13.7 (2.7); $t = -1.040$; $p = 0.305$).

DD patients reported more subjective EPS complaints. The total ESRS score was higher in the DD group than the SCZ group. More specifically, DD patients had more parkinsonian signs than SCZ patients. Similarly, DD patients were more frequently diagnosed with parkinsonism (table 1). Consistent with these results, PAS use (any PAS in the past week, in dollars) was positively correlated with subjective EPS ($r = 0.573$; $p = 0.003$), total EPS ($r = 0.496$; $p = 0.014$), parkinsonian signs ($r = 0.449$; $p = 0.028$), and global EPS ($r = 0.472$; $p = 0.020$) in the DD group.

A subanalysis was performed on cocaine ($n = 7$), as it has the worst consequences in schizophrenia.[8] Relative to the SCZ group, patients misusing cocaine had more EPS complaints, more total and global EPS, and increased parkinsonian signs, parkinsonism diagnoses, and signs of akathisia.

DISCUSSION

This cross sectional study sought to investigate the effects of PAS on EPS in schizophrenia. DD patients subjectively complained of more EPS. Objectively, the total ESRS score was higher in the DD group relative to the SCZ group. More specifically, DD patients displayed more parkinsonian signs and more parkinsonism diagnoses than SCZ patients. It is noteworthy that PAS use (any PAS) was positively correlated with subjective EPS, parkinsonian signs, and total and global EPS in the DD group. Also of interest was the fact that no patients in either group suffered from tardive dystonia or tardive dyskinesia. Dystonic and dyskinetic reactions were all acute. This result contrasts with the previous literature on the topic.[9 12]

Compared with abstinent patients, DD patients displayed greater EPS (especially parkinsonian signs). This result suggests that PAS may exert a detrimental impact on parkinsonian signs in schizophrenia patients. However, the cross sectional design of the study does not allow exclusion of the reverse explanation, namely, that schizophrenia patients may use PAS to get relief from their parkinsonian signs (self medication hypothesis).[18] More signs of akathisia were observed in cocaine misusers. Thus, cocaine may worsen akathisia in schizophrenia. This result is consistent with the pharmacology of cocaine, which blocks the dopamine and norepinephrine transporters in the motor pathways.[5] However, it must be considered that cocaine misusers were also misusing either alcohol or cannabis. Thus, the increased signs of akathisia in this group of misusers could be related to multi-substance misuse, not cocaine misuse per se.

Studies conducted on EPS in dual diagnosis schizophrenia have not been conclusive. Notably, most studies have not properly controlled for variables such as psychiatric symptoms, antipsychotic dosage, and anticholinergics. To overcome these limitations, we controlled for confounding effects by matching groups for age, sex, ethnicity, educational level, duration of illness, antipsychotic dosage, psychiatric symptoms, and anticholinergic drugs. Nevertheless, uncontrolled factors may have contributed to our results. For instance, affective symptoms were not assessed with a specific scale in the current study, but were controlled for with the PANSS ''affective factor''. Another study limitation was the small sample size. In addition, we cannot rule out the potential confounding effects of antipsychotic medication (even after

Table 1 Extrapyramidal symptoms in dual diagnosis schizophrenia

	Subjective		Total		Parkinsonism			Dystonia			Dyskinesia			Global		Akathisia		
	Mean	SD	Mean	SD	Mean	SD	Dx*	Mean	SD	Dx*	Mean	SD	Dx*	Mean	SD	Mean	SD	Dx*
(1) SCZ group (n = 17)	1.6	1.4	2.9	2.6	1.9	2.4	4	0.2	0.6	0	0.8	1.1	0	4	1.0	0.3	0.7	0
(2) DD group (n = 24)	3.2	2.6	9.3	11.0	8.7	9.3	17	0.3	1.4	1	0.3	1.1	1	4.2	1.8	0.7	1.0	1
(2a) Cocaine (n = 7)	3.9	3.8	16.9	16.8	14.7	13.6	6	0.4	0.8	1	1.0	2.6	1	5.6	2.6	1.3	1.3	1
F value (p value)																		
1 vs 2	4.687 (0.037)		5.513 (0.024)		8.657 (0.005)			0.071 (0.791)			2.417 (0.128)			0.123 (0.727)		2.050 (0.160)		
1 vs 2a	4.567 (0.044)		11.79 (0.002)		14.88 (0.001)			0.464 (0.503)			0.056 (0.815)			4.835 (0.039)		6.325 (0.020)		
χ^2 (p value)					8.912 (0.003)			0.726 (0.394)			0.726 (0.394)					0.726 (0.394)		
					7.889 (0.005)			2.534 (0.111)			2.534 (0.111)					2.534 (0.111)		

The first three rows are as given in the subheadings (mean, SD or mean, SD and Dx), while the last four are the results of the relevant statistical tests with p value in brackets. DD, dual diagnosis group; Dx, number of patients diagnosed with an EPS; ESRS, Extrapyramidal Symptoms Rating Scale; SCZ, schizophrenia only group; *Diagnoses established based on cutoff scores as defined by Chouinard and Margolese.[16]

controlling for chlorpromazine equivalency) and of PAS withdrawal, which may have mimicked iatrogenic EPS, as patients in the DD group were active misusers at the time of assessment.

Future longitudinal studies involving larger samples will be required to discriminate between the self medication hypothesis and the notion of deleterious effects of PAS on EPS in schizophrenia. Greater attention to cocaine and its consequences in schizophrenia is needed.

Our findings show significant relations between substance misuse and EPS in dual diagnosis schizophrenia patients, but cannot determine in which direction the relation may be, whether SUD lead to higher EPS or vice versa.

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