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ORIGINAL RESEARCH

Key Words: cannabis, cocaine, drug abuse, extrapyramidal side effects, neuroleptics, antipsychotics

Cocaine is a Major Risk Factor for Antipsychotic Induced Akathisia, Parkinsonism and Dyskinesia

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ABSTRACT ~ Objective: *To assess the relative contribution of different drugs of abuse to extrapyramidal side effects (EPS) of antipsychotic drugs.* ***Method:*** *106 consecutively contacted or admitted male patients in the Psychiatric Center of Surinam (PCS) with schizophrenia or a related disorder were included. Prevalence and severity of EPS were measured with the Unified Parkinson's Disease Rating Scale (UPDRS), the Abnormal Involuntary Movement rating Scale (AIMS), the Barnes Akathisia Rating Scale (BARS) and the Dystonia rating scale. Recent use of cigarettes, cannabis, alcohol, and cocaine were assessed. Standard multiple regression analyses were used to evaluate the relative contribution of above-mentioned drugs of abuse controlled for milligrams haloperidol equivalent a day and use of anticholinergic medication.* ***Results:*** *Recent cocaine use was significantly associated with severity of dyskinesia ($p = 0.001$), parkinsonism ($p = 0.007$), and akathisia ($p < 0.001$) ($n = 106$).* ***Conclusions:*** *Recent cocaine use is a major risk factor for antipsychotic induced EPS.* Psychopharmacology Bulletin. *2008;41(3):5–10.*

INTRODUCTION

The use of first generation antipsychotic medication is associated with extrapyramidal side effects (EPS), including dyskinesia, dystonia, parkinsonism, and akathisia.[1]

Risk factors for the development of EPS are gender, age, antipsychotic potency and dose, and a previous history of EPS.[2] A number of studies have suggested that drugs of abuse such as alcohol, cocaine, and cannabis are also risk factors for EPS.[3,4,5,6] However, in one report it was suggested that cannabinoids could be of therapeutic value for EPS.[7] Co-morbidity of schizophrenia and substance abuse is frequent.[8]

The aim of our study is to assess the relative contribution of recent drug abuse to the motor side effects of conventional antipsychotic drugs. We chose to study a consecutively contacted or admitted male patient population in Surinam since males are most prone to drug abuse, cannabis and cocaine are readily available and inexpensive in Surinam and since most patients in Surinam are treated with conventional antipsychotic drugs.

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METHODS

Male patients using antipsychotic drugs and with a diagnosis of schizophrenia or a related disorder, consecutively admitted to the observatory ward or consecutively contacted at the out-patient clinic of the Psychiatric Centre Surinam (PCS) during the period of March to June 2007, were included. Classification was made based on DSM IV-criteria by the treating psychiatrist. Local ethics committee approvals were obtained, and subjects gave their informed consent after a complete description of the study.

Data were collected on age, ethnicity, type, dose and duration of treatment with antipsychotic medication, and the use of other medication, cigarettes, alcohol, cannabis, and cocaine. Present drug use was defined on the basis of a positive answer to questions about substance use within the past week. To increase the validity of the self-report it was made clear to the patient that there were no adverse consequences for reporting drug use. The history of substance abuse was obtained by an interview that included age of onset and the type of drugs used. Only patients with a history of substance abuse of at least two years were included. Patient records and information from nurses and/or family were used to confirm the drug history. When drug abuse was denied by a patient we assumed that if there was confirmatory hetero-anamnestic information on substance abuse obtained from nurses or family, they were right.

Oral antipsychotic medication adherence of inpatients was verified using pill count by the nurses. Depot treatment was given according to a strict regime. All outpatients were given depot-treatment during their planned visit to the clinic. The dose of antipsychotic medication was converted into haloperidol dose equivalents per day.

EPS were rated by direct observation and examination using the following instruments: 1) the Unified Parkinson's Disease Rating Scale (UPDRS) measuring the degree of parkinsonism,[9] 2) the Abnormal Involuntary Movement rating Scale (AIMS) measuring the degree of dyskinisia,[10] 3) the Barnes Akathisia Rating Scale (BARS) measuring the degree of akathisia and dystonia.[11] All ratings were performed by the first author (AM). Movement disorder symptoms were not rated in retrospect but only when actually observed by the investigator.

Statistical analysis was performed using Pearson's correlation and standard multiple regression.

RESULTS

Hundred and six male patients (mean age 37, range 15–58 years), were included in the study. More than half (57.5%) of these patients

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was of Creole origin and 21.7% was of Indian, 12.3% of Javanese, 3.8% of Amerindian, and 4.7% of mixed origin.

One hundred and three patients were treated with first generation antipsychotic medication. Of these, 38 patients used haloperidol, pimozide or perfenazine orally and 60 patients were on depot treatment with flufenazine, haloperidol or fluspirileen. Five patients received first generation antipsychotic medication both orally and by depot treatment. The remaining three patients used atypical antipsychotics: olanzapine orally (n = 2) and olanzapine co-prescribed with depot treatment with penfluridol (n = 1). Mean dose in haloperidol equivalent per day was 7.7 mg (SD = 4.9 range: 1–20 mg). Mean duration of antipsychotic therapy was 13.2 years (SD = 5.6 range: 1 month to 32 years). Most patients (85%) were also treated with promethazine and/or benzodiazepines. Of the 106 patients, 79.2% smoked cigarettes, 57.5% used alcohol and 57.5% used cannabis. Cocaine was used by 33% of the patients. The route of drug administration for both cannabis and cocaine was always smoking. Cannabis was smoked in the form of marihuana and cocaine in the form of a cooked substance known as 'pits'.

Patients were not given anti-cholinergic medication on a prophylactic basis.

Standard Multiple Regression Analysis

Variables entered in multiple linear regression were: mg haloperidol equivalent a day, anticholinergic medication, smoking status and alcohol, cannabis and cocaine use in the last week.

Variables not entered in multiple linear regression because of insignificant correlation with EPS measures were: age, ethnicity, type of antipsychotic medication, duration of use of antipsychotic medication and age of onset of drug abuse (correlations varying from 0.02–0.09). Two-tailed alpha-levels were used (a = 0.05).

Cocaine made a significant contribution to the severity score of akathisia (unstandardized B = 2.77 SE 0.75, standardized Beta = 0.43 $p < 0.001$), dyskinesia (unstandardized B = 4.64 SE 1.33, standardized Beta = 0.40 p = 0.001) as well as parkinsonism (unstandardized B = 9.56 SE 3.46, standardized Beta = 0.32 p = 0.007).

Anticholinergic medication made a relatively weak but significant contribution to the severity score of dystonia (unstandardized B = 0.40 SE 0.19, standardized Beta = 0.21 p = 0.04).

DISCUSSION

The present study shows that recent cocaine use controlled for the recent use of other drugs, dose of antipsychotic drug and anticholinergic comedication is significantly associated with akathisia, dyskinesia

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TABLE 1

PEARSON'S CORRELATION (PCC) BETWEEN AKATHISIA, DYSKINISIA, PARKINSONISM, DYSTONIA AND VARIABLE*

TYPE EPS (TOTAL SCORE)	VARIABLE	PCC	P
Akathisia	mg haloperidolequivalent a day	0.27	0.003
	Cannabis use last week	0.19	0.03
	cocaine use last week	0.41	0.000
Dyskinesia	cigarettes use last week	0.26	0.003
	alcohol use last week	0.33	0.000
	cannabis use last week	0.34	0.000
	cocaine use last week	0.45	0.000
Parkinsonism	mg haloperidolequivalent a day	0.27	0.003
	cigarettes use last week	0.21	0.02
	alcohol use last week	0.17	0.05
	cannabis use last week	0.32	0.000
	cocaine use last week	0.41	0.000
Dystonia	mg haloperidolequivalent a day	0.17	0.04
	anticholinergic use	0.17	0.05
	cocaine use last week	0.17	0.04

*Pearson's correlation coefficient > 0.1.

and parkinsonism during treatment with first generation antipsychotic medication. This is an important finding since cocaine is frequently used by patients with schizophrenia.[8] Potvin et al. (2006)[12] found increased extrapyramidal symptoms in 17 patients with schizophrenia and a comorbid substance use disorder. They emphasize the importance of future studies involving larger samples. Our findings in a sample of 106 patients show that particularly recent use of cocaine rather than of cigarettes, marihuana or alcohol is associated with increased severity of EPS.

Since in Surinam drug abuse is limited almost exclusively to cocaine and cannabis it is unlikely that recent use of other drugs of abuse confound our results.

Our study has limitations. We classified patients as recent users of drugs on the basis of a positive answer by the patient to an interview question; a urine drug screening was not performed. A positive answer can be considered valid because there were no adverse consequences when drug-use was reported.[4] In case of denial by a patient we verified this by information obtained from family and nurses and assumed that their information was correct. However, information supplied by the family or nurses might also be inaccurate or subject to revision. Nevertheless, we think that this is unlikely given the close relationship between families and patients in Surinam.

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TABLE 2

STANDARD MULTIPLE REGRESSION EXAMINING RELATIONSHIP BETWEEN COCAINE USE LAST WEEK AND AKATHISIA, DYSKINESIA, PARKINSONISM AND DYSTONIA, CONTROLLED FOR TOTAL DOSAGE OF ANTIPSYCHOTIC DRUG IN MG HALOPERIDOLEQUIVALENT PER DAY, ANTICHOLINERGIC-, NICOTINE-, ALCOHOL-, AND MARIHUANA USE

VARIABLES	B	SE	β	P
Akathisia	2.77	0.75	0.43	0.000
Dyskinesia	4.64	1.33	0.40	0.001
Parkinsonism	9.56	3.46	0.32	0.007
Dystonia	0.29	0.19	0.19	0.12

Van Harten et al. (1998)[4] have suggested that cocaine is a major risk factor for acute dystonia. In addition, we now find that also akathisia, dyskinesia and parkinsonism are related to recent use of cocaine. In our studies, cocaine is not significantly related to the severity of dystonia controlled for other factors. However we found a relatively weak relationship between use of anticholinergic medication and severity of dystonia.

The relationship between use of anticholinergic medication and severity of dystonia might be explained by the association between the use of anticholinergic medication and the dose of antipsychotics; high doses are associated with dystonia and therefore dystonia is associated with the use of anticholinergic medication.

As well, patients using cocaine may be more liable to also use anticholinergics because anticholinergics are often a wanted substance for drug abusers.[13]

However, both these explanations are not applicable in our study because the results were controlled for the dose of neuroleptics and substance abuse.

Still it is possible that the observed association between the use of anticholinergics and dystonia may not be valid, because dystonia scoring may have been unreliable. Some of the patients faked dystonia to obtain anticholinergics from the nurses, as both patients and nurses confirmed. Although dystonia was only scored if symptoms were evident at the time of the interview and complaints about past episodes of dystonia were not taken into account, abovementioned malingering could have influenced the validity of assessment of dystonia.

Therefore, the relation of anticholinergics and dystonia is uncertain. Moreover, if it had been possible to reliably assess a history of dystonia, we might have been able to establish an association between cocaine and dystonia.

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In summary, this study provides evidence of cocaine being a main risk factor for EPS during treatment with first generation antipsychotic medication. Second generation antipsychotic medication might be considered in individuals who need antipsychotic treatment and who recently used cocaine. Alternatively, a lower dosage of first generation antipsychotic medication and/or prophylactic treatment with biperideen should be considered.✤

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