

The Impact of Cannabis Use on the Dosage of Antipsychotic Drugs in Patients Admitted on the Psychiatric Ward at the University Hospital of the West Indies

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ABSTRACT

Objective: To assess the impact of cannabis use on the efficacy of antipsychotic drugs in male subjects presenting to the University Hospital of the West Indies (UHWI) with psychotic episodes.

Methods: Male subjects, 18–40 years old, admitted to the psychiatric ward of the UHWI between February 2013 and May 2013, diagnosed with schizophrenia, schizophreniform disorder and who tested positive for Δ^9 -tetrahydrocannabinol were recruited for the study. On day one, consenting subjects were assessed using the Brief Psychiatric Rating Scale (BPRS). Patients were prescribed seven days of an oral antipsychotic medication (haloperidol, chlorpromazine, risperidone, quetiapine, olanzapine). Medicated subjects were then reassessed using the BPRS on days three and seven. Statistical analysis involved the use of Student's *t*-test and repeated measure analysis of variance.

Results: In total, 20 subjects were recruited (mean age = 26.00 ± 5.96 years). Subjects were grouped based on the daily chlorpromazine equivalent (CPZE) dose given on day one into CPZE1 (CPZE dose of 100–300 mg; $n = 8$) and CPZE2 (CPZE dose of 400–1250 mg; $n = 12$). There was no significant difference in the total BPRS score between the groups on day one (CPZE1 = 41.38 ± 16.47 versus CPZE2 = 49.42 ± 25.58 ; $p = 0.44$); similar findings were obtained for the positive (26.75 ± 9.27 versus 31.83 ± 17.30 ; $p = 0.46$) and negative (14.63 ± 7.73 versus 17.58 ± 9.74 ; $p = 0.48$) symptom component on the BPRS. For subjects in CPZE1, there was no significant decrease in total BPRS score [$F_{(2,21)} = 0.07$, $p = 0.93$] over the study period. For CPZE2, significant reduction in total BPRS scores was achieved [$F_{(2,33)} = 7.12$, $p = 0.01$], contributed by significant decrease in the positive [$F_{(2,33)} = 5.64$, $p = 0.02$] and negative [$F_{(2,33)} = 7.53$, $p = 0.01$] symptom components of the BPRS.

Conclusion: The findings of this study purport that male cannabis users presenting with psychotic disorders may not achieve optimal therapeutic benefit within seven days with CPZE doses ≤ 300 mg. As such, it appears that initiating treatment with CPZE doses of > 300 mg will provide better therapeutic outcomes for this patient population.

Keywords: Antipsychotics, cannabis, chlorpromazine equivalent dose

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INTRODUCTION

Significant advances have been made in the pharmacological management of psychiatric illnesses. Unfortunately, the positive impact of these advances has been at times affected by poor medication compliance, as well as genetic variability as it relates to the metabolism of psychotropic agents (1–3). This is a worrisome fact, for once a diagnosis of a psychotic illness has been made, use of antipsychotic medications is an eminent and almost unavoidable factor, unless contra-indicated (4, 5).

There is a high prevalence rate of cannabis use amongst Jamaican males, many of whom have been

diagnosed with a psychotic disorder and are receiving prescription medication for the same. A trawl of the literature indicated that information on the direct pharmacological interactions between cannabis and antipsychotic medications seem to be undocumented. One known fact, however, is that there are higher risks of exaggerated symptoms and/or relapse in patients diagnosed with psychosis who also have a history of concomitant cannabis use. However, the underlying pathophysiology is unclear (6, 7).

Anecdotally, it has been reported that subjects admitted to the psychiatric ward of the University Hospital of the West Indies (UHWI) with a history of cannabis use require a higher dose of antipsychotic medication in order to achieve adequate clinical control. The aims of this study were to ascertain if the doses of antipsychotic medications prescribed by the clinicians were determined by the severity of the patients' conditions and to assess the influence of cannabis use on the efficacy of antipsychotic drug therapy.

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SUBJECTS AND METHODS

A cross-sectional study was performed at the UHWI, Department of Psychiatry, from February 2013 to May 2013, and involved male subjects between 18 and 40 years old presenting with schizophrenia or schizophreniform disorder. Consequent to the diagnosis, subjects were prescribed the requisite antipsychotic medication. Subjects receiving any concomitant medication other than an antipsychotic were excluded from the study. The protocol was approved by the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee, and the relatives/guardians of subjects gave written informed consents for their participation.

Clinical assessment

Clinical presentation was assessed using the Brief Psychiatric Rating Scale (BPRS)–expanded version described by Dingemans *et al* (8) and Ventura *et al* (9, 10). This version evaluates 24 symptoms, subdivided into positive, negative, manic and depression/anxiety symptoms. Each symptom is rated on a seven-point severity scale, with no symptomatology rated as 1 and extremely severe rated as 7, and the scores are added to give a total score ranging from 24–168.

Protocol

Consented subjects were recruited for the study on day one of admission to the psychiatric ward. Urine was collected to group subjects as users and non-users of cannabis, using a SD-Bioline kit which tests for the main active metabolite of cannabis, Δ^9 -tetrahydrocannabinol (THC), giving a positive result when THC is greater than 50 ng/ml. The mental health professional attached to the study was blinded from the cannabis result. Baseline clinical assessment also included measurements of body weight, height, blood pressure, waist circumference, hepatic and renal function test. Age, living status and history of psychosis were also recorded. Each subject was included in the study for seven days.

Subjects were assessed using the BPRS-expanded version form, by the trained mental health professional, upon admission to the psychiatric ward (day one). All subjects received an initial treatment with haloperidol (10 mg intramuscularly) upon entry into the Accident and Emergency Department. Each subject was then orally medicated with an oral antipsychotic medication (haloperidol, chlorpromazine, risperidone, quetiapine, olanzapine) and was maintained on this initial medication for seven days with a dose increase as deemed necessary by the trained mental health professional. Most of the subjects in the study ($n = 13$, 65%) were prescribed an atypical antipsychotic medication (risperidone, quetiapine, olanzapine) while the remaining subjects ($n = 7$, 35%) were prescribed haloperidol, a typical antipsychotic medication. Using chlorpromazine equivalent (CPZE) conversion charts developed by Scott Woods in 2003 (11, 12), subjects were subdivided into two groups: CPZE1 (daily

CPZE dose of 100–300 mg; $n = 8$) and CPZE2 (daily CPZE dose of 400–1250 mg; $n = 12$). Subjects were reassessed using the BPRS on days three and seven for changes in BPRS. No other psychotropic medication was prescribed, with the exception of anticholinergics (cogentin) and/or antihistamines (diphenhydramine) for the alleviation of extrapyramidal symptoms. Subjects were also allowed to receive fluphenazine decanoate intramuscularly if needed.

Data analysis

Daily dosages of antipsychotic medications were converted to CPZE using drug comparison charts developed by Woods (11, 12). Response rate was calculated as (pre-treatment BPRS score minus post-treatment BPRS score/pre-treatment BPRS score) $\times 100$ and clinical improvement was measured as a response rate of $\geq 20\%$ (13). Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows with the level of significance set at $p < 0.05$.

RESULTS

In total, 24 subjects were recruited; however, four were excluded from analysis as their symptomatology necessitated drug regime changes outside of the study criteria. Of the 20 male subjects completing the study, the mean (\pm SD) age was 26.00 ± 5.96 years. The majority of the subjects were single ($n = 19$, 95%), received a secondary school level education ($n = 13$, 65%), were diagnosed with schizophrenia-paranoid type ($n = 17$, 85%) and used cannabis within one week of admission ($n = 13$, 65%) to the psychiatric ward. The demographic data for these patients are given in Table 1.

There was no significant difference in blood pressure, weight, height and abdominal circumference between the two groups. No derangement was observed in the renal function as the mean serum urea and creatinine concentrations were within the normal reference intervals of 2.5–6.7 mmol/L and 9–124 μ mol/L, respectively. However, as it relates to the hepatic function, the mean serum aspartate aminotransferase (AST) activity was approximately two times above the upper limit of the normal reference interval of 7–32 U/L. Additionally, the serum creatine phosphokinase (CPK) activity was approximately 9.5 times above the upper reference limit, as the normal reference interval for males is 40–240 U/L (Table 1). Statistical analysis of the AST and CPK enzymes at baseline showed no significant difference between CPZE1 and CPZE2.

Table 2 shows the antipsychotics given to each subject in the study and the CPZE conversions. Twelve subjects received CPZE2 and eight received CPZE1. For the CPZE1 group, there was no significant difference in the CPZE dose from day one to day seven. For the CPZE2 group, the finding was the same, although the patient receiving haloperidol had a reduction in dose from day one.

Table 1: Baseline (day one) demographic information of patients enrolled in the study

Demographic data	Total (n = 20)
Schizophrenia, n (%)	Paranoid type = 17 (85%); Disorganized type = 1 (5%)
Schizophreniform disorder	2 (10%)
Age, years (mean ± SD)	26.00 ± 5.96
Ethnicity	Afro-Caribbean
Marital status, n (%)	Single = 19 (95%); Married = 1 (5%)
Highest education level, n (%)	Primary = 2 (10%); Secondary = 13 (65%); Tertiary = 5 (25%)
Occupation, n (%)	Employed = 7 (35); Unemployed = 8 (40%); Student = 5 (25%)
Age of first use of cannabis, years (mean ± SD)	14.23 ± 3.17
Age of first psychotic episode, years (mean ± SD)	22.20 ± 4.16
Living status, n (%)	Alone = 6 (30%); With family = 13 (65%); Other = 1 (5%)
Body weight, kg (mean ± SD)	66.76 ± 13.32
Height, cm (mean ± SD)	171.71 ± 7.16
Waist circumference, cm (mean ± SD)	77.78 ± 8.96
Blood pressure, mmHg (mean ± SD)	Systolic pressure: 119.05 ± 19.12 Diastolic pressure: 74.25 ± 8.12
Direct bilirubin (mmol/L)	5.44 ± 2.92
Total bilirubin (mmol/L)	14.67 ± 6.95
Alkaline phosphatase (U/L)	59.06 ± 15.32
Gamma glutamyl transferase (U/L)	26.85 ± 10.95
Aspartate aminotransferase (U/L)	72.08 ± 69.13
Creatine phosphokinase (U/L)	2279.89 ± 1289.24
Lactate dehydrogenase (U/L)	302.50 ± 151.57
Albumin (g/L)	42.53 ± 3.56
Sodium (mmol/L)	138.06 ± 2.11
Potassium (mmol/L)	4.05 ± 1.14
Chloride (mmol/L)	103.35 ± 3.69
Calcium (mmol/L)	2.37 ± 0.09
Phosphorus (mmol/L)	1.39 ± 1.35
HCO ₃ (mmol/L)	20.08 ± 2.50
Urea (mmol/L)	4.00 ± 1.11
Creatinine (mmol/L)	81.06 ± 17.79
Total protein (g/L)	72.76 ± 4.45
Total globulins (g/L)	48.06 ± 70.30

Table 2: Comparison of chlorpromazine equivalent (CPZE) doses between dosing groups (CPZE1, CPZE2) of prescribed antipsychotic agents on assessment days

Antipsychotic drug CPZE dose/mg	Day 1	Day 3	Day 7
CPZE1 (n = 8)			
Risperidone	5.25 ± 1.49	5.25 ± 1.49	5.25 ± 1.49
Total CPZE dose	262.50 ± 74.40	262.50 ± 74.40	262.50 ± 74.40
CPZE2 (n = 12)			
Haloperidol (7)	18.57 ± 4.76 928.57 ± 133.63	17.86 ± 2.67 892.85 ± 133.63	17.86 ± 2.67 892.85 ± 133.63*
Quetiapine (1)	300 400	300 400	600 800
Olanzapine (4)	22.50 ± 5.00 450.00 ± 100.00	20 400	20 400
Total CPZE dose	725.00 ± 311.52	687.50 ± 272.30	720.83 ± 258.02

*represents statistically significant decrease in the haloperidol CPZE dose over the study period ($p = 0.03$)

The Figure shows that there was no significant difference in the total BPRS score between the groups (CPZE1 = 41.38 ± 16.47 versus CPZE2 = 49.42 ± 25.58 ; $p = 0.44$); similar findings were obtained for the positive (26.75 ± 9.27 versus 31.83 ± 17.30 ; $p = 0.46$) and negative (14.63 ± 7.73 versus 17.58 ± 9.74 ; $p = 0.48$) symptom components of the BPRS.

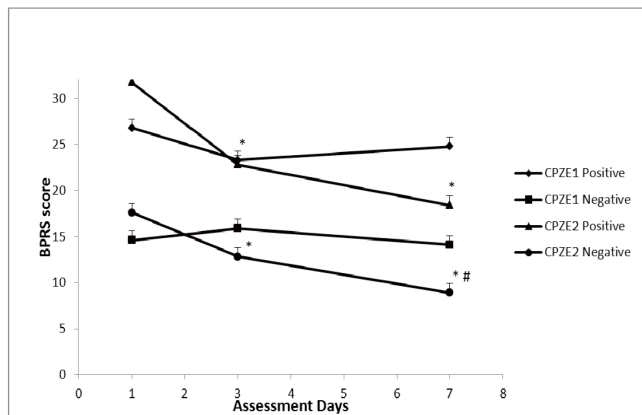


Figure: Positive and negative symptoms of the Brief Psychiatric Rating Scale (BPRS) measured on days one, three and seven of the study with chlorpromazine equivalent dosing groups (CPZE1 and CPZE2) dose ranges prescribed in the ward.

*represents significant difference in the days three and seven mean BPRS scores compared to the day one scores for the CPZE2 dose range.

#represents the statistical difference seen in the day three versus day seven BPRS scores.

For CPZE1, the day three mean BPRS score was 39.13 ± 10.86 and the day seven mean BPRS score was 38.88 ± 15.16 , however, the change was not significantly different from day one [$F_{(2,21)} = 0.07$, $p = 0.93$]. Similar findings were obtained for the positive [$F_{(2,21)} = 0.514$, $p = 0.62$] and negative [$F_{(2,21)} = 0.66$, $p = 0.55$] symptom components of the BPRS for this group.

For CPZE2, the significant decrease by day three to 35.50 ± 18.68 ($p = 0.01$) through day seven to 27.33 ± 14.88 ($p = 0.002$) contributed to a significant decrease in mean BPRS score across the study period [$F_{(2,33)} = 7.12$, $p = 0.01$]. Further assessment of the change in total BPRS score showed that the improvement in the score was contributed by a significant decrease in the positive symptom component of the BPRS [$F_{(2,33)} = 5.64$, $p = 0.02$], attributed to a significant decrease from day one to day three ($p = 0.036$) through to day seven ($p = 0.005$). There was also a significant decrease in the negative symptom components of the BPRS [$F_{(2,33)} = 7.53$, $p = 0.01$], attributed to significant change from day one to day three ($p = 0.012$) through to day seven [$p = 0.002$] (Figure).

Using a change in total BPRS of $\geq 20\%$ as the measure of clinical improvement, by day three, 25% (2/8) of subjects receiving CPZE1 showed a clinical improvement to the medication compared to 38.5% (5/12) receiving CPZE2. These proportions were not significantly different (Fisher's

exact $p = 0.642$). However, by day seven, while clinical improvement remained at only 25% in the CPZE1 group, clinical improvement was seen in the majority, 83.3% (10/12), of subjects for the CPZE2 group (Fisher's exact $p = 0.015$).

DISCUSSION

In this study, the BPRS was the instrument used to determine the severity of the psychotic symptoms being experienced by the subject as well as the efficacy of the prescribed treatment regime. The highest BPRS scores were obtained on day one, with a gradual decrease in the BPRS scores recorded over the study period. These findings indicated that irrespective of the type of antipsychotic drug (haloperidol, quetiapine, olanzapine, risperidone), the prescribed treatment regime was effective.

Biochemical analysis revealed an elevation in the hepatic enzymes AST and CPK activity upon admission to the study (day one). This finding is consistent with documented studies, as these enzymes are reportedly high during the acute stages of psychosis (14–19). Statistical results showed that this elevation was not significantly different between the dosing groups (CPZE1 and CPZE2).

After conversion of the prescribed medications to the relevant chlorpromazine equivalents, subjects were grouped into those receiving 100–300 mg and those receiving 400–1250 mg (20). No significant difference was noted in the total BPRS scores between the dose ranges on day one. The subjects prescribed CPZE2 had significantly better outcomes on days three and seven follow-up than subjects prescribed CPZE1. Even though, from the findings, CPZE doses ≤ 300 mg may be the minimal effective doses in patients (21), it appears that this dose is suboptimal and caution should be taken when prescribing doses < 300 mg to male cannabis users with a diagnosis of schizophrenia or schizophreniform disorder. Clinical assessment of the subjects further underscored this finding as most of the subjects who received > 300 mg CPZE attained clinical improvement by day seven compared to only two of eight subjects showing clinical improvement with the lower CPZE dose.

This study provides preliminary evidence that cannabis users diagnosed with a psychotic disorder may require larger doses of medication to effect eradication of symptoms compared to non-cannabis users diagnosed with a psychotic disorder. The findings are limited by the small sample size and absence of a cannabis naïve group in the study (THC < 50 ng/ml on presentation). Another limitation includes possible inter-rater variability as different mental health professionals were involved in the scoring of symptoms on the BPRS over the assessment days. It is, however, clear that the findings provide a direct link to the doses of drugs prescribed to patients with schizophrenia and schizophreniform disorder and the BPRS scores measured over a seven-day period.

In conclusion, doses of medication prescribed to patients are directly related to the control of the severity of the psychotic impairments. In patients exposed to cannabis use, the recommended starting dose should be > 300 mg CPZE to provide better therapeutic outcomes.

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