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The effects of cannabidiol on behavioural and oxidative stress parameters induced by prolonged haloperidol administration

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Original Article

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Abstract

Objectives: We investigated the influence of oral cannabidiol (CBD) on vacuous chewing movements (VCM) and oxidative stress parameters induced by short- and long-term administration of haloperidol in a rat model of tardive dyskinesia (TD). *Methods:* Haloperidol was administered either sub-chronically via the intraperitoneal (IP) route or chronically via the intramuscular (IM) route to six experimental groups only or in combination with CBD. VCM and oxidative stress parameters were assessed at different time points after the last dose of medication. *Results:* Oral CBD (5 mg/kg) attenuated the VCM produced by sub-chronic administration of haloperidol (5 mg/kg) but had minimal effects on the VCM produced by chronic administration of haloperidol (50 mg/kg). In both sub-chronic and chronic haloperidol groups, there were significant changes in brain antioxidant parameters compared with CBD only and the control groups. The sub-chronic haloperidol-only group had lower glutathione activity compared with sub-chronic haloperidol before CBD and the control groups; also, superoxide dismutase, catalase, and 2,2-diphenyl-1-picrylhydrazyl activities were increased in the sub-chronic (IP) haloperidol only group compared with the CBD only and control groups. Nitric oxide activity was increased in sub-chronic haloperidol-only group compared to the other groups; however, the chronic haloperidol group had increased malondialdehyde activity compared to the other groups. *Conclusions:* Our findings indicate that CBD ameliorated VCM in the sub-chronic haloperidol group before CBD, but marginally in the chronic haloperidol group before CBD. There was increased antioxidant activity in the sub-chronic group compared to the chronic group.

Significant Outcomes

- Prolonged administration of haloperidol for 3 months produced a more sustained form of VCM
- Sustained administration of haloperidol was associated with reduced antioxidant activity suggesting increased oxidative stress with increased duration of administration of haloperidol
- CBD had minimal impact on VCM induced by chronic administration of haloperidol compared to VCM induced by sub-chronic administration of haloperidol

Limitations of Study

- We did not undertake a pharmacokinetic–pharmacodynamic (PK/PD) analysis and did not ascertain drug concentrations and their effects via different routes of administration.
- We could not use the same route of administration for the sub-chronic and chronic administration of haloperidol because repeated IM administration of haloperidol for 21 days or IP administration for 60 days can lead to local complications such as pain, cellulitis, and fibrous myopathy (Burnham *et al.*, 2006).
- We used male rats only because most of the recent literature on animal models of TD used male rats or mice (Busanello *et al.*, 2012; Peres *et al.*, 2016; Sonego *et al.*, 2018), which would allow us to draw comparisons with other studies. We acknowledge that not including female rats may introduce a potential bias.
- Lastly, due to technical difficulties, we measured neurochemical parameters in whole brain tissue instead of specific brain regions.

Introduction

Tardive dyskinesia (TD) is a difficult-to-treat chronic involuntary movement disorder associated with dopamine receptor blocking agents, mostly antipsychotics (Rana *et al.*, 2013; Cloud *et al.*, 2014; Kim *et al.*, 2014) and anti-emetics (e.g., metoclopramide) (Merrill *et al.*, 2013). Onset is usually delayed with orofacial dyskinesia being the most prominent presentation although athetosis, dystonia, chorea, motor tics, and myoclonus are also common (Mahmoudi *et al.*, 2013; Kim *et al.*, 2014; Kamyar *et al.*, 2016; Cornett *et al.*, 2017). Effective management of emergent TD is important because the symptoms and signs impact negatively on the quality of life of patients and on medication compliance (Lee *et al.*, 2009; Syu *et al.*, 2010 Su *et al.*, 2012; Creed *et al.*, 2012; Chang & Fung, 2014; Kim *et al.*, 2014).

The risk of developing TD increases with age. Other factors associated with TD include the presence of affective symptoms, female sex, organic brain disorders, and the presence of negative and cognitive symptoms in schizophrenia (Woerner *et al.*, 1998; Syu *et al.*, 2010; Rana *et al.*, 2013; Sarró *et al.*, 2013; Kim *et al.*, 2014; Ryu *et al.*, 2015; Solmi *et al.*, 2018). The prevalence of TD is also higher in patients on typical compared to those on atypical antipsychotics (Rana *et al.*, 2013 Kim *et al.*, 2014; Chang & Fung, 2014; Cloud *et al.*, 2014; Cornett *et al.*, 2017), with a global mean prevalence rate of 30% with conventional antipsychotics and 21% for atypical antipsychotics (Carbon *et al.*, 2017). While it was previously thought that atypical antipsychotics would ameliorate the risk of TD, recent data have been less promising (Mahmoudi *et al.*, 2013; Cloud *et al.*, 2014; Shireen, 2016; Bordia *et al.*, 2016; Loughlin *et al.*, 2019; Sartim *et al.*, 2016; Patterson-Lomba *et al.*, 2019).

In low- and middle-income countries, typical antipsychotics often constitute most antipsychotic prescriptions, for example, in Nigeria this is almost 80%, with trifluoperazine being the most prescribed antipsychotic (54.2%) (Bakare *et al.*, 2011; Onah *et al.*, 2018). The prevalence of TD may also be higher than in western countries. A recent study at a Nigerian teaching hospital reported a prevalence of 5.8% (Nkporbu *et al.*, 2016), while an earlier study at a psychiatric hospital recorded a prevalence of 27% (Gureje, 1987). The high rate of polypharmacy prescription patterns in Nigeria and in sub-Saharan Africa in general may also contribute to the development of adverse drug effects, including TD, because in most cases polypharmacy consists of a long-acting intramuscular depot combined with either a typical or atypical antipsychotic drugs (Adeponle *et al.*, 2008; Tesfaye *et al.*, 2016; Igbinomwanhia *et al.*, 2017).

Although the pathophysiology of TD is still being unravelled, studies have implicated dopamine receptor supersensitivity (DRS) with receptor upregulation, γ-aminobutyric acid (GABA) depletion, cholinergic deficiency, lower expression of serotonin (5HT-2A) receptors, neurotoxicity and oxidative stress, changes in synaptic plasticity, defective neuroadaptive signalling, and lack of antipsychotic metabolising enzymes, as putative mechanisms (Rana *et al.*, 2013; Cornett *et al.*, 2017; Creed *et al.*, 2012; Cloud *et al.*, 2014; Kim *et al.*, 2014; Bordia *et al.*, 2016). Genetic factors may also play an important role in TD with documented associations between TD and polymorphisms of the dopamine D_3 (DRD3), serine-9-Glycine (Ser9Gly), heparan sulfate proteoglycan 2, perlecan (HSPG2), and serotonin 2A and 2C receptor genes (Graff-Guerrero *et al.*, 2009). In addition, Val66Met, a naturally occurring polymorphism in the brain-derived neurotropic factor gene, may be associated with the development and severity of TD in Caucasians, and the transcriptional factor Nur77, a central regulator of T cell immunometabolism (also known as NGFI-B or Nr4a1) has also been implicated in the development of TD (Tiwari *et al.*, 2008; Chang & Fung, 2014; Cornett *et al.*, 2017; Syu *et al.*, 2010; Liebmann *et al.*, 2018).

A prolonged dosing regime is strongly associated with increased receptor occupancy levels and chronic blockade of dopamine D_2 and D_3 receptors (Naidu & Kulkarni, 2001a; Margolese *et al.*, 2005; Kasantikul & Kanchanatawan, 2007; Seigneurie *et al.*, 2016). Persistent receptor blockade has also been linked to the upregulation of dopamine receptors and DRS (Nel & Harvey, 2003; Ginovart *et al.*, 2009; Yin *et al.*, 2016). This blockade also leads to increased dopamine turnover which is associated with overproduction of free radicals, such as the quinone/semiquinone metabolites by monoamine oxidases and auto-oxidation of dopamine molecules (Wyatt, 1999; Cho & Lee, 2013). This induces apoptosis and neuronal death of the GABA interneurons that regulate balance between direct and indirect basal ganglia pathways (Gunne *et al.*, 1984; Margolese *et al.*, 2005; Gittis *et al.*, 2011), leading to symptoms of TD. The same overproduction of free radicals can also damage the glutamatergic neurons, disrupting the synaptic plasticity of glutamatergic synapses on striatal interneurons, and causing an imbalance between direct and indirect basal ganglia pathways, thus producing abnormal output to the sensorimotor cortex (Cadet & Perumal, 1990; Teo *et al.*, 2012).

Cannabidiol (CBD) is a phytocannabinoid with multiple complex actions on the central nervous system (Zuardi, 2008; Peres *et al.*, 2018). Though CBD's mechanism of action is not fully understood, studies have suggested that it is a non-competitive negative allosteric modulator of CB_1 and CB_2 receptors (Peres *et al.*, 2018; Laprairie *et al.*, 2015; Martínez-Pinilla *et al.*, 2017). It is also an agonist at the transient receptor potential channels of the vanilloid subtype 1 ($TRPV_1$) (Bisogno *et al.*, 2001). CBD inhibits enzymatic hydrolysis and uptake of anandamide and regulates mitochondria activity; all these actions mediate the anti-inflammatory and antioxidant effects of CBD (Bisogno *et al.*, 2001; Peres *et al.*, 2018; Valvassori *et al.*, 2013; Campos *et al.*, 2016). It also enhances neurotransmission mediated by the serotonin 5-HT_{1A} receptor by acting as an allosteric modulator at this receptor, and this action may be responsible for its anxiolytic effects (Rock *et al.*, 2012; Sartim *et al.*, 2016; Lee *et al.*, 2017).

In addition, CBD regulates the peroxisome proliferator-activated receptor γ (PPARγ) and PPARγ ligands are known to display anti-inflammatory actions (O'Sullivan *et al.*, 2009; Sonego *et al.*, 2018). CBD also antagonises D_2 receptors (Graff-Guerrero *et al.*, 2009), which may contribute to its antipsychotic effects (Seeman, 2016).

We hypothesised in an animal model of TD that chronic exposure to haloperidol through IM administration of slow-releasing haloperidol for 3 months would lead to more sustained VCM compared with sub-chronic IP haloperidol administered for 21 days. Our prototype antioxidant (CBD) would, therefore, be less effective in a slow-releasing IM haloperidol group compared to a sub-chronic IP haloperidol group. We also proposed that there would be an increase in oxidative stress in the slow-releasing IM haloperidol group compared to the IP haloperidol group, as measured by several oxidative stress indices.

Materials and methods

Animals

Male adult Wistar rats ($n = 53$) were obtained from a colony of the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos,

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Nigeria. The animals were kept in clean polypropylene cages in well-ventilated and hygienic compartments, maintained under standard environmental conditions, and fed with standard rodent pellets (Ladokun Feed Plc., Ibadan, Nigeria) and water *ad libitum*. The animals were acclimatised for a period of 2 weeks before experimental procedures were undertaken in accordance with the United States National Institutes of Health Guidelines for Care and Use of Laboratory Animals in Biomedical Research (National Research Council, 2011). The study is the second component of a larger study approved by the Institutional Review Board (IRB) of NIMR, Yaba, Lagos, Nigeria (IRB/16/329), and the Stellenbosch University Health Research Ethics Committee: Animal Care and Use (SU-ACUD16-00137).

Drugs

CBD [(-)-Cannabidiol, GMP (Cannabidiolum); CBD] (VAKOS X, a.s., Permova 28a, Praha, Czech Republic) was supplied in fine granule form with the amount administered weekly calculated and dissolved in 70% ethanol, as recommended by the manufacturer, and diluted with distilled water. CBD was administered orally. Rapid-acting parenteral haloperidol at 5 mg/ml was administered intraperitoneally, while slow-releasing parenteral haloperidol 50 mg/ml (Janseen Pharmaceuticals, Beerse, Belgium) was administered through the intramuscular route.

Experimental design

There were six experimental groups ($n = 53$): sub-chronic haloperidol administration (SC-HAL) ($n = 9$); sub-chronic haloperidol before CBD administration (SC-HAL-CBD) ($n = 10$); CBD only ($n = 9$); chronic haloperidol administration (CH-HAL) ($n = 8$); chronic haloperidol before CBD administration (CH-HAL-CBD) ($n = 7$) and the control group ($n = 10$).

The administration of pharmacological agents was as follows: SC-HAL (haloperidol at 5 mg/kg IP), SC-HAL-CBD (haloperidol 5 mg/kg IP before administration of CBD at 5 mg/kg p.o.), CBD (CBD at 5 mg/kg p.o.), control (2 ml distilled water p.o.), CH-HAL (Haloperidol decanoate at 50 mg/kg IM), and CH-HAL-CBD (haloperidol decanoate at 50 mg/kg IM before administration of CBD at 5 mg/kg p.o.) (Table 1).

For the SC-HAL, CBD, and the control groups, the agents were administered once daily for 21 days (Sasaki *et al.*, 1995; Naidu & Kulkarni, 2001a, 2001b, Bishnoi & Boparai, 2012). A dose of 5 mg/kg of haloperidol was administered IP (Bishnoi and Boparai, 2012) in SC-HAL group. Effective doses of CBD in rats' range between 2.5 and 10 mg/kg (Guimarães *et al.*, 1990). VCM was assessed at 8 h, 24 h, and 8 days after the last dose of medication. Assessment on day 8 was to ensure that the VCM model was established.

For SC-HAL-CBD, the first pharmacological agent (haloperidol) was administered for 21 days, and the second pharmacological agent (CBD) was commenced 24 to 48 h after the first was discontinued and this was administered for a further 21 days. VCM was assessed after the last dose of pharmacological agent at 8 h, 24 h, and on the 8th day. The rats in SC-HAL-CBD were pre-treated with haloperidol to induce VCM before the administration of CBD to ascertain if CBD ameliorated haloperidol-induced VCM.

For the C-HAL group, slow-releasing IM haloperidol decanoate 50 mg/kg was administered monthly (Andreassen *et al.*, 2001) on three consecutive occasions and VCM was assessed on day 28, and day 36 after the last administration of IM haloperidol. For the CH-HAL-CBD, slow-releasing intramuscular haloperidol decanoate 50 mg/kg monthly for three consecutive months was also administered, but administration of CBD 5 mg/kg for 21 days was commenced 24 to 48 h after the last dose of intramuscular haloperidol. VCM was assessed at 24 h and 8th day after the last dose of CBD (Table 1).

SC-HAL and SC-HAL-CBD were classified as IP haloperidol groups and received IP haloperidol either only or in combination with CBD, while CH-HAL and CH-HAL-CBD were classified as IM haloperidol groups and received IM haloperidol either only or in combination with CBD.

Vacuous chewing movement assessment

Vacuous chewing movement (VCM, mouth openings in the vertical plane not directed toward physical material) was assessed by placing each animal in an individual transparent glass plexiform cage. Each animal was allowed to acclimatise for 5 min before counting started. The number of VCM was counted for 10 min (Crowley *et al.*, 2012). The VCM results reported corresponding to the last VCM measurement taken before the animals were killed for each group.

Animals were killed 24 h after all the behavioural assessment were carried out for all groups. They were first anesthetised with phenobarbitone before cervical dislocation and then dissected by opening the abdomen. The brain was isolated and dissected on ice where 10% w/v of brain sample (0.03 M sodium phosphate buffer, pH 7.4) was homogenised. The homogenates generated from processed brain tissue were then used for oxidative stress indices determination.

The following antioxidant indices were determined spectrometrically: malondialdehyde (MDA), glutathione (GSH), catalase activity (CAT), superoxide dismutase activity (SOD), nitric oxide (NO) scavenging activity, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay. Methodologies used in determining antioxidant indices were described in detail in our previously published study (Kajero *et al.*, 2020).

Statistical analysis

Data were analysed using the IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY: IBM Corp.). Continuous variables such as VCM, behavioural assays and antioxidant levels, when normally distributed were presented using means and standard deviations as measures of central tendency and dispersion. Kolmogorov–Smirnov test was used to identify skewed variables. A comparison of the equality of means between groups was done using a one way-ANOVA test. When the *F*-statistic was significant (<0.05), depending on the violation of the homogeneity of variance, the Tukey's HSD test or Games Howell post hoc test was used to identify the differences between groups. Where the data were not normally distributed, a comparison of medians was done using the Kruskal–Walli's test. Box and whisker plots were used in the presentation of continuous variables as a figure.

Results

Effects on VCMs

There was a significant difference in mean VCM count before and after the administration of medications in the SC-HAL group (<0.001) and CH-HAL group (<0.001). There was also a

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Table 1. Pharmacological administration schedule

Groups	Pharmacological agent	Administration schedule	VCM counts
SC-HAL	Haloperidol 5 mg/kg IP only	HAL for 21 days	8 h, 24 h, and 8 days after last dose of HAL
SC-HAL-CBD	Haloperidol 5 mg/kg IP before administration of CBD 5 mg/kg p.o.	HAL for 21 days then CBD for 21 days	8 h, 24 h, and 8 days after last dose of CBD
CBD	CBD 5 mg/kg p.o. only	CBD for 21 days	8 h, 24 h, and 8 days after last dose of CBD
Control	2 ml distilled water p.o.	21 days	8 h, 24 h, and 8 days after last dose of distilled water
CH-HAL	Haloperidol decanoate 50 mg/kg IM only	HAL decaonate for 90 days	Day 28 and day 36 after the last dose of HAL
CH-HAL-CBD	Haloperidol decanoate 50 mg/kg IM before administration of CBD 5 mg/kg p.o.	HAL decaonate for 90 days then CBD for 21 days	24 h and 8 days after the last dose of CBD

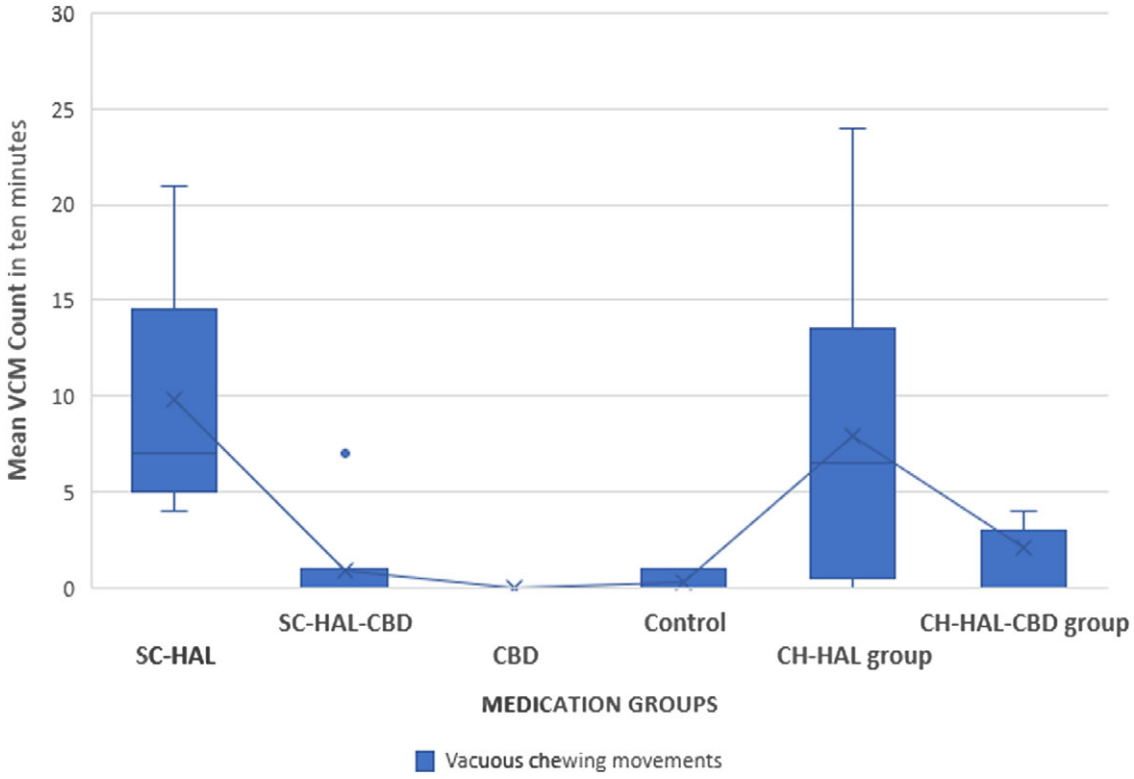

Fig. 1. Vacuous chewing movements.

statistically significant difference in mean VCM among the six groups ($p < 0.000$) (Fig. 1).

SC-HAL: sub-chronic haloperidol administration; SC-HAL-CBD: sub-chronic haloperidol before CBD administration; CBD: cannabidiol; CH-HAL: chronic haloperidol administration; CH-HAL-CBD: chronic haloperidol before CBD administration; Control : 2 ml distilled water.

Post hoc analysis revealed a significant difference between SC-HAL and SC-HAL-CBD groups ($p = 0.015$), SC-HAL and CBD groups ($p = 0.009$), SC-HAL and control groups ($p = 0.011$), SC-HAL and SC-HAL-CBD groups ($p = 0.036$), CBD and CH-HAL groups ($p = 0.002$), and CH-HAL and CH-HAL-CBD groups ($p = 0.049$).

Antioxidant assays

Brain oxidative stress indices

In the brain, antioxidant indices in the IP haloperidol and the IM haloperidol groups were compared with the oral CBD only and control groups. There were significant changes in brain oxidative stress indices between the sub-chronic (IP) haloperidol (SC-HAL), chronic (IM) haloperidol (CH-HAL), oral CBD, and control: CAT ($p = 0.000$), SOD ($p = 0.000$), GSH ($p = 0.000$), (scavenging activity in DPPH assay) ($p = 0.000$), NO ($p = 0.000$), MDA ($p = 0.000$). The sub-chronic (IP) haloperidol-only (SC-HAL) group showed higher activity of antioxidant parameters relative to the other groups, except in respect of GSH where the SC-HAL group had

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Table 2. Brain antioxidant indices

Brain antioxidant	SC-HAL Mean ± SD	SC-HAL-CBD Mean ± SD	CBD Mean ± SD	Control Mean ± SD	CH-HAL Mean ± SD	CH-HAL-CBD Mean ± SD	*p* value
CAT (μmol/ml/min/mg pro)	56.5 ± 15.9	26.0 ± 10.1	14.1 ± 5.5	27.5 ± 6.1	23.6 ± 6.3	28.2 ± 11.0	0.000
GSH (μmol/ml)	10.5 ± 2.0	19.8 ± 6.5	18.9 ± 7.9	44.7 ± 17.2	22.0 ± 15.5	19.4 ± 7.1	0.000
NO (μmol/dl)	41.9 ± 4.7	17.0 ± 5.1	19.7 ± 5.1	12.6 ± 3.8	15.7 ± 1.6	17.8 ± 5.0	0.000
MDA (μmol/ml)	5.5 ± 1.9	1.7 ± 1.0	3.1 ± 2.2	2.3 ± 0.8	10.7 ± 3.4	1.5 ± 1.2	0.000
SOD (μmol/ml/min/mg pro)	9.1 ± 2.0	3.0 ± 1.0	4.6 ± 2.1	4.6 ± 0.8	4.6 ± 1.7	3.2 ± 0.9	0.000
DPPH (IC50/μg/ml)	78.5 ± 9.2	59.0 ± 6.5	75.3 ± 3.4	57.8 ± 15.0	27.4 ± 7.9	77.2 ± 4.0	0.000

significantly lower activity compared with the other groups (Table 2).

Post hoc comparison of sub-chronic administration of haloperidol groups (SC-HAL and SC-HAL-CBD) and chronic administration of haloperidol groups (CH-HAL and CH-HAL-CBD) with oral CBD only and control groups.

Brain SOD

Post hoc analysis revealed significant differences between SC-HAL and SC-HAL-CBD groups ($p = 0.001$), SC-HAL and CBD groups ($p = 0.015$), SC-HAL and control groups ($p = 0.006$), SC-HAL and CH-HAL groups ($p = 0.010$), SC-HAL and CH-HAL-CBD groups ($p = 0.001$), and SC-HAL-CBD and control groups ($p = 0.022$).

Brain CAT

There were significant difference between SC-HAL and SC-HAL-CBD groups ($p = 0.014$), SC-HAL and CBD groups ($p = 0.001$), SC-HAL and control groups ($p = 0.018$), SC-HAL and CH-HAL groups ($p = 0.007$) SC-HAL and CH-HAL-CBD groups ($p = 0.035$), and CBD and control groups ($p = 0.001$).

Brain GSH

SC-HAL group had a significantly lower activity of brain GSH than other groups with significant between-group differences for the SC-HAL and SC-HAL-CBD groups ($p = 0.014$), and SC-HAL and control groups ($p = 0.001$). SC-HAL-CBD and the control groups ($p = 0.011$), CBD and control groups ($p = 0.009$), and control and CH-HAL-CBD groups ($p = 0.012$).

Brain NO

Post hoc analysis revealed significant differences in NO activity between SC-HAL and SC-HAL-CBD groups ($p = 0.000$), SC-HAL and control groups ($p = 0.000$), the SC-HAL and control groups ($p = 0.000$), SC-HAL and CH-HAL groups ($p = 0.000$), SC-HAL and CH-HAL-CBD groups ($p = 0.000$), and CBD and control groups ($p = 0.037$).

Brain MDA

Post hoc analysis revealed significant differences in MDA activity between SC-HAL and SC-HAL-CBD groups ($p = 0.001$) and SC-HAL and control groups ($p = 0.004$), SC-HAL and CH-HAL (SCHAL < CHAL, $p = 0.031$), and SC-HAL and CH-HAL-CBD groups ($p = 0.001$). There was also a statistically significant difference in MDA activity between SC-HAL-CBD and CH-HAL groups ($p = 0.001$), CBD and CH-HAL groups (CBD < CHAL, $p = 0.002$), control and CH-HAL groups (control < CHAL, $p = 0.001$), and CH-HAL and CH-HAL-CBD groups ($p = 0.001$). CH-HAL had the highest activity followed by SC-HAL.

Brain scavenging activity (DPPH assay)

There were significant differences between SC-HAL and SC-HAL-CBD groups ($p = 0.001$), SC-HAL and control groups ($p = 0.016$), SC-HAL and CH-HAL groups ($p = 0.000$), SC-HAL and CBD groups ($p = 0.000$), SC-HAL-CBD and CH-HAL groups ($p = 0.000$), SC-HAL-CBD and CH-HAL-CBD groups ($p = 0.000$), CBD and control groups ($p = 0.042$), CBD and CH-HAL groups ($p < 0.001$), control and CH-HAL groups ($p = 0.001$), control and CH-HAL-CBD groups ($p = 0.024$), and CH-HAL and CH-HAL-CBD groups ($p = 0.024$).

Discussion

This study is the second report in a series of studies on the effectiveness of CBD in ameliorating symptoms of VCM induced by haloperidol in an animal model of TD. We investigated the effects of chronic exposure to haloperidol in the form of IM-administered slow-releasing haloperidol without any other pharmacological agent for 3 months and of sub-chronic administration of IP haloperidol without any other pharmacological agent for 21 days, on the severity of VCM. We then investigated the effectiveness of CBD in ameliorating VCM induced by chronic and sub-chronic exposure to haloperidol. We also evaluated the influence of chronic and sub-chronic administration of haloperidol on oxidative stress indices.

Effects of interventions on VCM

Our results show that sub-chronic haloperidol only produced significantly more VCM than the other groups except for chronic haloperidol only. We can also infer from our study that CBD when given after the administration of sub-chronic haloperidol ameliorates haloperidol-induced VCM. We previously established the ability of CBD to prevent VCM when administered simultaneously with haloperidol (Kajero *et al.*, 2020). Attenuation of haloperidol-induced VCM by CBD may be explained by its antioxidant and neuroprotective effects (Malfait *et al.*, 2000; Peres *et al.*, 2016). CBD also promotes neurogenesis (Valvassori *et al.*, 2011; Gallegos *et al.*, 2015) and may interact with the $5HT_{1A}$ and $5HT_{2A}$ receptor subtypes in the basal ganglia (Russo *et al.*, 2005) to ameliorate dopaminergic system dysfunction (Gomes *et al.*, 2013).

We further observed that CBD barely mitigated chronic haloperidol administration-induced VCM. This is most likely due to the chronic exposure to haloperidol leading to prolonged receptor occupation and consequently increased dopamine turnover in regions of the brain with high density of catecholamine, such as the basal ganglia, and overproduction of free radicals with damage to neuronal cells (Wyatt, 1999; Margolese *et al.*, 2005; Gittis *et al.*, 2011; Cho & Lee, 2013, leading to symptoms of TD. Previous

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studies have investigated acute parenteral administration of reserpine (Peres *et al.*, 2016), acute (IP) haloperidol (Gomes *et al.*, 2013), and sub-chronic administration of IP haloperidol (Sonego *et al.*, 2016).

In respect of IP and oral haloperidol administered for 21 days, in accordance with our previous report (Kajero *et al.*, 2020), the occupation of D_2 receptors may not have been prolonged enough to induce severe oxidative stress and permanent damage to the GABA interneurons and glutamatergic neurons. The VCM we observed with these two routes of administration may be due to blockage of D_2 receptors in the caudate, putamen, and the globus pallidus (Rupniak *et al.*, 1986; Van Harten *et al.,* 1996), and complex reciprocal interactions between dopamine and acetylcholine (ACH) receptors. These complex interactions may lead to hypercholinergic activity in the striatum and may more closely mirror early-onset dyskinesia in humans than late-onset dyskinesia (Waddington, 1990; Egan *et al.*, 1996; Marchese *et al.*, 2004; Blanchet *et al.*, 2012).

Antioxidant indices in the brain: (sub-chronic and chronic haloperidol groups compared with CBD only and controls)

We found an elevation of SOD activity in the haloperidol-only group compared to the other groups. This may represent a compensatory mechanism to oxidative stress produced by sub-chronic haloperidol administration. SOD acts as first line of defence against oxidative stress by converting super oxide radicals to hydrogen peroxide which is, in turn, converted to water and oxygen by catalase and glutathione peroxidase (Dakhale *et al.*, 2004; Kunz *et al.*, 2008). We also observed an increase in the activity of SOD in the control group compared to sub-chronic haloperidol before CBD. The activity of SOD as a scavenger of free radicals may increase in the presence of excessive production of free radicals as the system attempts to maintain a healthy redox balance (Harris, 1992; Dakhale *et al.*, 2004; Boskovic *et al.*, 2011). The relatively low SOD activity in the group that received sub-chronic haloperidol before adjunctive CBD and in the CBD-only group suggests that CBD may ameliorate the oxidative stress produced by haloperidol by modifying redox imbalance (Atalay *et al.*, 2020), possibly through some other mechanism.

We did not find any significant difference when chronic haloperidol only and chronic haloperidol before CBD groups were compared, suggesting chronic administration of haloperidol only did not exhibit more SOD activity than chronic haloperidol before CBD, unlike what we observed between sub-chronic haloperidol only group and sub-chronic haloperidol before CBD. Administration of CBD after chronic haloperidol administration also did not have any influence on SOD production, unlike what we observed in sub-chronic haloperidol before CBD. Boskovic *et al.* (2011), in a clinical study, observed a decrease in antioxidant enzyme activity with prolonged use of antipsychotics and increased age in patients with schizophrenia.

Catalase is an efficient antioxidant produced in the peroxisome (small membrane-enclosed organelles important in metabolic reactions) with a remarkably high turnover rate and may have been induced in the IP haloperidol-only group to catalyse the conversion of increased hydrogen peroxide (H_2O_2) produced by SOD to water and oxygen (Sies, 2015; Kurutas, 2016). CBD may have effectively reduced the free radical production in the group administered sub-chronic haloperidol before adjunctive CBD. Popovic *et al.* (2009) observed an increase in catalase activity in their study examining the effects of acute administration of haloperidol in animals in a stressful environment. Though their dose of haloperidol differed from our study, most other studies have reported a decreased level of catalase activity in haloperidol-only groups (Naidu *et al.*, 2002; Patil *et al.*, 2012; Thakur *et al.*, 2015). Differences in dosage, duration, and sequence of medication administration may influence enzyme activity in these studies.

There was no significant difference in catalase activity between the chronic haloperidol only, CBD only, and control groups, suggesting that chronic haloperidol only did not induce increase CAT activity unlike what we observed with sub-chronic haloperidol only where CAT was increased to compensate for the increase in oxidative stress. The brain has 50 times lower catalase and SOD than the liver (Cobley *et al.*, 2018), and this may have limited its ability to increase CAT and SOD production in response to increased oxidative stress over a long period. No prior studies of the influence of CBD on behavioural and biochemical parameters associated with long-term administration of IM haloperidol decanoate have, to our knowledge, been published.

Glutathione peroxidase (GPx) is the enzyme responsible for the conversion of reduced GSH to the oxidised form (GSSG) with the help of hydrogen peroxide which is converted to water and oxygen in the process (Burk & Hill, 2010; Ursini & Maiorino, 2013). Increased activity of GPx will therefore lead to a decrease in the level of GSH. The low level of reduced GSH in the sub-chronic haloperidol only compared to the sub-chronic haloperidol with adjunctive CBD groups suggests increased activity of GPx. It is plausible that the three antioxidants (SOD, CAT, and GSH) acted in concert to keep free radicals at low levels. Other investigators observed an enhancement of the activity of GPx and reductase enzymes by CBD (Massi *et al.*, 2006).

The control group had a higher GSH level than the other groups indicating reduced GPx activity and less oxidative stress in the control group. There was no significant difference between chronic haloperidol only and chronic haloperidol before CBD groups in contrast to the sub-chronic haloperidol only and sub-chronic haloperidol before CBD groups, suggesting CBD did not have an influence on GPx activity or GSH level in chronic haloperidol administration. There is a paucity of studies in this regard though an earlier study also observed a decrease in antioxidant enzymes and non-enzymatic GSH in the brain after long-term administration of haloperidol (Boskovic *et al.*, 2013).

Pro-oxidants (sub-chronic and chronic haloperidol groups compared with CBD only and control)

NO is an unusual messenger molecule with multiple molecular targets; it normally controls neurotransmission and vascular tone. It is also important in the regulation of gene and messenger ribonucleic acid (mRNA) transcription and can promote post-translational modifications of proteins (O'Dell *et al.*, 1991; Schuman & Madison, 1991; Pozdnyakov *et al.*, 1993; Pantopoulos & Hentze, 1995; Khan *et al.*, 1996; Gudi *et al.*, 1999; Förstermann & Sessa, 2012). Under physiologic conditions, NO (a free radical) and its metabolites are neutralised through reactions with various thiols (e.g., GSH) to form stable S-nitrosothiols. If produced in excess because of lipid peroxidation, thiols may be overwhelmed leading to increased production of free radicals and oxidative stress (Gegg *et al.*, 2003; Andreazza *et al.*, 2008).

The higher activity of NO in the brain observed in the sub-chronic haloperidol-only group in relation to other groups indicates increased oxidative stress in this compared to other groups. The reduced NO activity in the CBD-only group and the sub-

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chronic group with adjunct CBD administration suggests that CBD can ameliorate oxidative stress when combined with haloperidol by reducing NO production. Some investigators have reported on the ability of CBD to inhibit inducible NO synthase and therefore reduce NO production (Costa *et al*., 2004; Esposito *et al*., 2006; Rajesh *et al*., 2007; Chen *et al*., 2016).

The chronic haloperidol administration-only group had significantly less NO activity than the sub-chronic haloperidol-only group and did not have more NO activity than either chronic haloperidol before CBD, CBD only, or the control indicating chronic haloperidol group did not alter NO balance or CBD did not affect NO activity in the IM haloperidol groups. Some investigators have reported that chronic administration of haloperidol followed by withdrawal is associated with reduced NO and lower striatal cGMP levels (Iwahashi *et al*., 1996; Harvey & Bester, 2000). In contrast, other studies found up-regulation of NOS activity in the rat striatum after dopamine receptor blockade, suggesting that this may contribute to the motor side effects of antipsychotic agents (Morris *et al*., 1997; Sammut *et al*., 2007). More studies are needed to clarify the relationship between prolonged administration of haloperidol and NO.

There is evidence that increase in free radicals can lead to dysfunction of oxidative stress enzymes causing membrane damage and elevating lipid peroxidation products such as MDA, especially in the spinal fluid (Zhang & Yao, 2013). Interestingly, we observed higher MDA activity in the chronic haloperidol-only group compared to other groups, sub-chronic haloperidol group also had more MDA activity compared to other groups except for the chronic haloperidol-only group, suggesting a greater increase in free radical production and lipid peroxidation compared to other interventions. This is in the same direction as other studies (Consroe *et al*., 1991; Kudo & Ishizaki, 1999; Patil *et al*., 2012; Kamyar *et al*., 2016; Zendulka *et al*., 2016). It is also an indication that increased MDA activity in the brain may be associated with prolonged duration of administration of haloperidol and severity of VCM. We also observed a decrease in MDA in the sub-chronic (IP) haloperidol before CBD group compared to sub-chronic haloperidol-only group indicating CBD inhibited lipid peroxidation and probably prevented membrane damage when given after haloperidol.

The chronic haloperidol before CBD group MDA measurements also had less activity than the chronic haloperidol-only group, further confirming the ability of CBD to inhibit lipid peroxidation in various organs, as described in other studies (Luvone *et al*., 2004; Mechoulam *et al*., 2007; Pisanti *et al*., 2017). These observations support our hypothesis that neuronal cell damage is induced by prolonged administration of haloperidol. There are no other studies, as far as we are aware, of the effects of CBD on chronic administration of haloperidol on the brain's antioxidant system.

DPPH (2,2-diphenyl-1-picrylhydrazyl) (sub-chronic and chronic haloperidol groups compared with CBD only and control)

The DPPH assay was developed to evaluate free radical scavenging activity of antioxidants in organic solvents but has been used to assess antioxidant capacity of hydrolysed porcine tissues (Sanchez-Moreno *et al*., 1998; Kedare & Singh, 2011; Damgaard *et al*., 2014). In our study, we used DPPH to assess the total antioxidant activity in the brain. In the sub-chronic group, brain homogenates scavenging activities in DPPH were increased in the sub-chronic haloperidol-only group compared to the sub-chronic haloperidol before CBD group, suggesting an increase in antioxidant activity (SOD and CAT in this study) as a compensatory mechanism for the increased free radical production observed in this group. Rao & Balachandran (2002) proposed that disequilibrium between free radical metabolism and the antioxidant system can produce excessive ROS.

The ROS system contains enzymes, such as SOD, GPx, and CAT. DPPH, a stable radical (Kedare & Singh, 2011), interacts with the ROS antioxidant system. Sub-chronic haloperidol only in our study generated more oxidative enzymes compared to sub-chronic haloperidol before CBD, the control, and chronic haloperidol only. This may explain why scavenging activities were increased in our brain samples with sub-chronic haloperidol administration only. Our observations of low scavenging activity in DPPH in the brain in the chronic haloperidol-only group compared to other groups is not surprising as SOD and CAT activities in the chronic haloperidol only group were consistently low. We also detected a high scavenging activity in the chronic haloperidol before CBD group which confirms reduced antioxidant enzyme activity in this group and at the same time suggests that CBD contributed to antioxidant activities in the IM haloperidol before CBD group. This confirmed our earlier suggestions that prolonged administration of haloperidol maintained a consistently high level of free radicals and diminished the ability of the brain to generate antioxidant enzymes (Boskovic *et al*., 2013). CBD probably helped to alleviate the increased MDA activity observed in the chronic haloperidol only.

In summary, we found that CBD ameliorates established VCM induced by sub-chronic haloperidol administration but was marginally effective in ameliorating VCM induced by chronic haloperidol administration, confirming our first hypothesis that prolonged administration of haloperidol through the IM route induced a more severe form of VCM compared to 21-day IP haloperidol administration. We can thus infer that there is an association between long-term administration of haloperidol and increased activity of MDA and reduced activity of antioxidants. Therefore, slow-releasing chronic haloperidol diminished the ability of the brain to compensate for persistent oxidative stress. Our results also suggest that CBD may be exerting its effect primarily by modifying the activities of GSH and MDA.

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Authors Contributions. Both Jaiyeola kajero and Soraya Seedat conceived and design the work. Jaiyeola Kajero, Abidemi Akindele, and Oluwagbemiga Aina were responsible for data collection, analysis, and interpretation. Jaiyeola Kajero was responsible for drafting the article. Soraya Seedat, Jude Ohaeri, and Abidemi Akindele were responsible for critical revision of the article and Soraya Seedat was responsible for final approval of the version to be published.

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Conflicts of Interest. None.

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Animal Welfare Ethical Statement. The animals were properly housed in clean polypropylene cages with well-ventilated and hygienic compartments, fed with standard rodent pellets (Ladokun Feed Plc., Ibadan, Nigeria) and water *ad libitum,* and kept in surroundings appropriate to their species and acclimatised for a period of 2 weeks before experimental procedures were undertaken in accordance with the United States National Institutes of Health Guidelines for Care and Use of Laboratory Animals in Biomedical Research (National Research Council, 2011). The study was approved by the Institutional Review Board (IRB) of NIMR, Yaba, Lagos, Nigeria (IRB/16/329) and Stellenbosch University's Health Research Ethics Committee: Animal Care and Use (SU-ACUD16-00137).

Ethical Standards. The authors assert that all procedures contributing to this work comply with the South African National Standard (SANS) on the care and use of laboratory animals.

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