# Investigation of the Effects of Cannabidiol and Cannabinol (CBN) on Post Traumatic Stress Disorder in a Clinical Trial.

INTRODUCTION

Economic and political crises on the African continent have led to deep social conflicts which frequently degenerates to armed struggles between different sections of the society (Stewart, 2002) These multiple crises frequently produce psychological stressors which impact negatively on the mental health of the people (Sheikh et al.,2016; Anhange et al.,2016). If the stressors are severe and life threatening some genetically predisposed individuals could have traumatic experiences which manifest clinically as symptoms of anxiety associated with specific behaviours and physiological responses (Smoller , 2016). Natural and man- made disasters can also be described as traumatic events which can have psychological consequences (Steinglass and Gerrity, 1990; McFarlane and Papay, 1992; Riaz et al.,2015). For most people the psychological trauma is restricted to an acute, transient disturbance, though limited these reactions are quite unpleasant and can be grouped into three main domains : (i) reminders of the exposure (including flashbacks, intrusive thoughts, nightmares); (ii) activation (including hyperarousal, insomnia, agitation, irritability, impulsivity and anger); and (iii) deactivation (including numbing, avoidance, withdrawal, confusion, derealization, dissociation, and depression), these reactions leads to mild functional impairment in the majority of people. However, for a sizable minority the psychological trauma is prolonged (Sherin et al., 2011). Post- traumatic stress disorder (PTSD) is the diagnostic entity for a specific set of prolonged reactions to psychological trauma.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) introduced a new category called Trauma- and Stressor-Related Disorders and all diagnosis terms in this classification including PTSD require exposure to a traumatic or stressful event as a diagnostic criterion, PTSD diagnosis also requires that there should be an intrusion symptom, an avoidance symptom, two symptoms related to negative alterations in cognitions and mood, alterations in arousal and reactivity are also necessary and the duration should be more than one month. All these must be associated with distress and functional impairment and symptoms are not likely to be associated with medication, substance use, or other illness (APA, 2013).

PTSD is the most common complication of psychological trauma (Caffo and Belaise, 2003). The National Comorbidity Survey–Replication in the United States conducted in 2001–2002, estimated that the 12-month prevalence of PTSD in the U.S. adult population was 3.6% and that the lifetime prevalence was 6.8% (Harvard Medical School,2007a, b). The prevalence of post-traumatic stress disorder was found to be 22.8% among survivors of road traffic accident in Ethiopia (Yohannes et al 2018) and 26.7% in Enugu, Nigeria (Iteke et al., 2011). In Nigeria there is no national data yet on prevalence of PTSD but a study in Jos township during the time of ethno-religious crises in the state where Jos township is the capital, found a high prevalence rate of 23.5% among medical students (Nwoga et al ., 2016) Another study in the same city among the residents found a crude prevalence of 41% after the same crisis (Tagurum et al.,2015). An understanding of the pathophysiology of PTSD is necessary to explain the high prevalence of the disorder in conflict zones.

Cortisol is important in the aetiology of PTSD but it’s probably the end stage neurotransmitter released in a cascade of events that involved several neurotransmitter system including the noradrenergic, serotonergic, endogenous cannabinoid and opioid systems and the hypothalamic-pituitary adrenal (HPA) axis that connects the central nervous system (CNS) to the endocrine system (Bailey et al.,2013). Noradrenaline and adrenaline are released immediately after exposure to a life-threatening stressor, cortisol is released some few minutes later to modulate the activities of the two neurotransmitters (Morris and Rao, 2013). Hyperarousal and reexperiencing symptoms of PTSD are related to alterations of noradrenergic activity (O Donnell et al., 2004). The adrenoceptors (ARs) which noradrenaline and adrenaline acts upon, have been the targets of drug development. Post-traumatic and prophylactic administration of propranolol have not yielded consistent results but the noradrenaline transporter (NET) targets like atomoxetine have shown some promises (Spencer et al.,2006), but there is no published clinical trial yet on the effectiveness of atomoxetine in PTSD (Sofuoglu et al., 2014).

Animal and human studies have implicated the serotonergic system in the aetiology of PTSD, as alteration of the 5-HT1A and 5HT1B receptor activitieshave been observed in PTSD (Morris and Rao, 2013). Selective serotonin reuptake inhibitors (SSRI) increase the extracellular level of the neurotransmitter serotonin available in the brain to act on the 5HTs receptors by limiting its reabsorption (Stahl, 1998). A Cochrane review which encompasses 35 RCTs and 4597 participants however did not support the use of the Selective serotonin reuptake inhibitors (SSRI) as first-line medication in PTSD. Brady et al (2005), conducted an RCT involving 94 individuals with comorbid PTSD and alcohol disorder (AD), they concluded that sertraline was not better than placebo for reducing PTSD and AD symptoms.

Venlafaxine, a selective serotonin and noradrenaline reuptake inhibitor (SNRIs) have also been effective in reducing re-experiencing and avoidance/numbing symptoms (Davidson et al.,2006; Davidson et al 2006). A randomized pragmatic trial however did not find any difference on the effects of venlafaxine and sertraline on PTSD when the two were compared (Sonne et al., 2014), so the search for a an effective pharmacotherapeutic agent for PTSD continues.

Evidence is accumulating for the role of endogenous cannabinoids (eCB), anandamide (AEA) and 2-arachidonolyglycerol (2-AG) in PTSD (Bailey et al., 2013). The endogenous cannabinoids exert their influence through the cannabinoid (CB) receptors (CB1, CB2), which are believed to be important in stress responses including PTSD circuit (Krebs-Kraft et al.,2010). Animal and human studies found an inverse relationship between PTSD and anandamide levels in the brain (Kathuria et al 2003; Bailey et al 2013). CB1 are in abundance in the limbic system where they modulate a broad range of behaviours which are closely linked to PTSD symptoms, this include mood, stress, anxiety, learning, memory and extinction of fear (Viveros et al.,2005: Martins et al.,2002; Ameri et al.,1999). Unfortunately, CB1 receptor inverse agonists such as rimonabant and Δ9- tetrahydrocannabivarin (THCV) have been associated with emergence of negative mood symptoms and suicidality. Drugs that modulate CB1 receptors directly may therefore not be appropriate for PTSD (Bailey et al., 2013). Cannabidiol (CBD) and Cannabinol (CBN) do not directly bind to CB1 receptors, while CBD inhibit Fatty acid indole acetic acid (FAAH) an enzyme responsible for the degradation of eCBs in the brain to increase the anandamide level in the brain (Mechoulam et al.,2000), Cannabinol exert its effect on CB2 receptors, these receptors are known to mediate inflammation and are able to inhibit stress- related signals that lead to chronic inflammation (Gertsch 2008). Sustained cortisol release induced by life threatening stressors leads to chronic inflammation which alters the function and structure of parts of the brain responsible for the maintenance of normal emotional reactions to events. CB2 activation by cannabinol may help reduce this chronic inflammation. Both CBD and CBN are also not psychoactive (Andre et al.,2016; Mechoulam et al.,2000; McCallum et al., 1975), which makes them the ideal plant-based cannabinoids to investigate. It is therefore important to investigate the effect of cannabidiol and cannabinol on PTSD in a clinical trial.

**LITERATURE REVIEW**

**Cannabinoids**

The term cannabinoids describe a group of chemical compounds that activate cannabinoid receptors on cells that repress neurotransmitter release in the brain. Cannabinoids include endogenous cannabinoids, Phyto cannabinoid and synthetic cannabinoids (Patcher et al., 2006). The most studied cannabinoids are the Phyto cannabinoids; tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) (Lambert and Fowler 2005).

Cannabinol

Cannabinol is a metabolite of tetrahydrocannabinol (THC), with potential immunosuppressive and anti-inflammatory activities. Cannabinol preferentially binds to the cannabinoid G-protein coupled receptor CB2, which is mainly expressed on a variety of immune cells, such as T-cells, B-cells, macrophages and dendritic cells. Stimulation of CB2 receptors by cannabinol may both trigger apoptosis in these cells and inhibit the production of a variety of cytokines. Cannabinol exerts minimal affinity for CB1 and has a weak effect on the central nervous system (Andre et al.,2016).

Cannabidiol (CBD)

The pharmacological actions of this compound have been explored by different investigators more than any other cannabinoid with exception of THC, it is the most abundant cannabinoid in the cannabis sativa plant after THC and may be up to 40% in some preparation, it is therefore likely to be responsible for the pharmacological actions that contradicts those of THC. Inhibition of anandamide uptake and the prevention of enzymatic hydrolysis of anandamide have been observed in vitro. If these effects are observed in vivo, we may expect enhancement of endocannabinoid action (Bisongo et al., 2001). CBD is also said to have direct effect on mitochondrial dependent Ca homeostasis. This may be the mechanism by which CBD exerts its neuroprotective effects (Ducan et al., 2009).

**Pathophysiology of Post-Traumatic Stress Disorder**

Chronic dysregulation of the system that response to perceived threats can lead to the symptoms of PTSD (Sherin and Nemeroff 2011). This system is made up of neuroendocrine, neurochemical and neuroanatomic components. Abnormalities of these neurobiological features have been identified in PTSD patients or animal models of PTSD (Sherin and Nemeroff 2011).

Low levels of cortisol have been hypothesized to be a pre-existing risk factor that engenders the development of PTSD. The basic functions of glucocorticoids/cortisol include modification of metabolism, immune system and brain function to promote adaptation or removal of the stressors and provision of negative feedback control of the HPA axis which regulates corticotropin-releasing hormone (CRH) and Adrenocorticotropic hormone (ACTH) release (Sherin and Nemeroff 2011). Hypocortisolism will therefore lead to sustained release of the CRH which promotes hippocampal atrophy, a cardinal feature of PTSD (Bremner et al., 2008; Levy and Tasker 2012). CRH is postulated to be involved in abnormal stress encoding and fear processing (Yehuda et al.,1998).

CRH and NE also interact with each other to increase fear conditioning and encoding of emotional memories, enhance arousal and vigilance, and integrate endocrine and autonomic responses to stress. The glucocorticoids inhibit this action of CRH and NE, hypocortisolism will therefore promote unopposed autonomic and neuroendocrine responses to stress, as well as augmented fear conditioning and traumatic memory consolidation (De Quervain, 2008). Increased dopamine level has also been observed in PTSD and this is linked to fear conditioning in the mesolimbic system (Sherin and Nemeroff, 2011).

Gama aminobutyric acid (GABA) and glutamate are important in the regulation of HPA axis (Levy et al., 2012) as they are the key neurotransmitters in memory formations (Reul and Nutt, 2008). Exposure to stressors and the subsequent release of glucocorticoids activates glutamate release in the brain, glutamate binds to N-methyl D-aspartate (NMDA) receptors which are linked to learning and memory and are therefore important in the formations of traumatic memories in PTSD (Reul and Nutt, 2008). NE regulates CRH neuronal activities by modulating glutamate and GABA release. Glutamate also reduced the tonic inhibition of GABA on the CRH/NE circuits involved in mediating fear and stress responses (Levy and Tasker 2012). So, we have a system in which the major neurotransmitters in the brain interact with each other to modified reactions of an individual to stress.

The serotonergic (5-HT) receptors are important in cognition, emotional processing and behavioral regulation (Cools., et al 2008). The receptors are in abundance in the amygdala, a brain region important in the understanding of fear response and PTSD aetiology (Zanoveli et al.,2009; Muller et al.,2011) Decrease in concentrations of serotonin(5HT) in the dorsal and median raphe, has been observed in PTSD and its associated with disturbance of the dynamic between amygdala and hippocampus and increased in anxiety associated with hypervigilance, startle, impulsivity, and memory intrusions (Sherin and Nemeroff 2011).

Apart from CRH, neuropeptides (NPY) also influenced the development of PTSD. NPY may have a positive effect on the symptoms of PTSD because it has anxiolytic and can ameliorate stress. It exerts it effects by suppressing the CRH/NE circuits involved in stress and fear responses and inhibiting the release of NE from sympathetic neurons. A deficiency of NPY may promote maladaptive stress responses and contribute to the development of PTSD (Yehuda 2006; Rasmusson et al.,2000)

Endogenous opioid peptides including the endorphins and enkephalins act on three subtypes of receptors; δ (encephalin preferring), κ (dynorphin preferring) and μ (morphine preferring) The dynorphin/κ opioid receptor (κ-OR) most likely have a role in the production of stress-induced behaviours because endogenous opioids exert inhibitory influences on the HPA axis. PTSD patients exhibit increased CSF β-endorphin levels, suggesting increased activation of the endogenous opioid system. Alterations in endogenous opioids may be involved in certain PTSD symptoms such as numbing, stress-induced analgesia, and dissociation. (Dhawan et al., 1996; Sauriyal et al 2011).

The findings of neuroimaging studies implicated the hippocampus, amygdala, and prefrontal cortex in the neuropathology of PTSD (Starcevic 2016). The amgydala is involved in normal emotional reactions to objective stimuli and perception it is also indicated in the processing of emotional aspect of memory and had been observed to be hyperactive in individuals exposed to traumatic events. PTSD may be linked to the failure of the prefrontal cortex to ameliorate the hyperarousal and distress that are mediated through the amygdala in response to reminders of the traumatic event (Bremner 2006, Filipovi et al 2011, Milad et al, 2009).The hippocampus , a brain area involved in learning and memory is adversely affected by stress with associated memory deficits. This may be because it contains high level of glucocorticoid receptors which make it vulnerable to chronic stress as the sustained release of glucocorticoids during stress is associated with hippocampal atrophy (Joel 2008).

The prefrontal cortex is the seat of executive functions in humans and it also help suppresses memories, its volume and functioning are reduced in people with PTSD (Liston et al.,2006; Rajkowaska et al., 1997). Globus pallidus an important subcortical grey structure is involved in the regulation of sleep and sleep disorders are prominent in PTSD. It has been postulated that sleep disorders can induce hypoxia in the brain which could affect blood flow into the brain leading to brain atrophy. The brain neurotransmitters are also affected by sleep deprivation and long-term cortisol release can also have adverse effects on the Globus pallidus (Goelman et al., 2014).

Structural plasticity observed in the hippocampus and the amygdala has been linked to the influence of sex hormones and this may contribute to gender differences in the brain’s response to fear stimuli (McEween, 2001 ; Schienle et al .,2005)

Despite the role of external stressors in the development of PTSD there is evidence that genetic factors modified the reactions of individual to life threatening events. Decrease hippocampal volume and exaggerated amygdala reactivity, two important endophenotypes of PTSD may be hereditary (Gillbertson et al., 2002; Hariri and Mattay, 2002). Another study linked a polymorphism in the dopamine (DA) transporter gene to PTSD risk (Segman et al., 2002). A low expression variant of the serotonin transporter is a risk factor for the endophenotypes of PTSD (Lesch et al., 1996). A genetic variation of the glucocorticoid receptor protein FKBP5 influenced risk of developing PTSD in victims of child abuse (Binder et al., 2008).

**PTSD and the Endocannabinoid system**

The endocannabinoid system is a neuroactive lipid signaling system in the brain (Trezza and Patrizia, 2013), which regulate affective states and participate in memory consolidation, retrieval, and extinction by modulating neurotransmitters release ( Fernandez-Ruiz et al., 2000; Harkany et al.,2007; Trezza and Patrizia, 2013) The system is made up of three basic components; the cannabinoid receptors (CB1 and CB2), endocannabinoids (Anandamide(AEA) and 2-acetylglycerol (2-AG)) and the enzymatic machinery for endocannabinoid synthesis and degradation (Piomelli, 2003; Di Marzo et al., 2005).

The endocannabinoids controlled the release of neurotransmitters especially NE and serotonin at the synapse. AEA and 2-AG levels in specific arears of the brain such as the amygdala are increased by chronic exposure to glucocorticoids but CRH signaling decreases AEA signaling. Stress exposure causes CRH release and this will lead to increase activity of fatty acid amide hydrolase (FAAH) the enzyme responsible for the break down of AEA thereby reducing AEA and since AEA modify the release of the neurotransmitters NE, serotonin and glutamate there will be uncontrolled release of the neurotransmitters (Gray et al., 2015, 2016; Natividad et al, 2017; Hill et al, 2013a; Morena et al, 2016b), and early consolidation of contextual fear conditioning (Burman et al,2016).

2-AG is synthesized by the conversion of diacylglycerol to 2-AG by the enzyme diacylglycerol lipase (DAGL), and its metabolism is primarily driven by the enzyme monoacylglycerol lipase (MAGL; (Blankman and Cravatt, 2013)). MAGL inhibition leading to increase 2-AG production is associated with moderate reductions in unconditioned anxiety-like behaviors in normal situations (Almeida-Santos et al, 2013; Bluett et al, 2017; Busquets-Garcia et al, 2011; Kinsey et al, 2011; Morena et al, 2016a; Sciolino et al, 2011). These anxiolytic effects are mediated through CB1 and CB2 receptors (Busquets-Garcia et al.,2011).

Exposure to chronic stress can produce neuroinflammatory changes in the brain (Zoppi et al.,2014) and some studies have proposed a relationship between inflammatory systems and PTSD (Hill et al.,2018). CB2 receptors are prominent on microglia in the brain and the activation of the receptors have been linked to reduced inflammatory processes, including suppressing the release of pro-inflammatory cytokines (Hill et al., 2018). Inhibition of FAAH or MAGL, to elevate AEA or 2-AG signaling, respectively, can also ameliorate inflammatory processes, (Grabner et al, 2016; Hernangomez et al., 2012; Kerr et al, 2012, 2013; Malek et al, 2015; Roche et al, 2008; Tham et al, 2007). Increase activities of AEA and 2-AG at CB2 receptors has been found to reduce the neuroinflammatory response produced by repeated stress exposure (Zoppi et al, 2014).

Cannabidiol, as described above is a non-psychoactive cannabinoid. Its’ known to inhibit anandamide uptake and prevent enzymatic hydrolysis of anandamide (Bisongo et al., 2001). It also has direct effect on mitochondrial dependent Ca homeostasis which may be the mechanism by which it exerts its neuroprotective effects (Ducan et al., 2009). It is therefore expected to have effects on the cognitive and anxiety symptoms of PTSD if we take the above review into consideration.

Cannabinol, as mentioned above is also non-psychoactive and exerts it effects on CB2 receptors and given the ability of these receptors to inhibit stress- related signals that lead to chronic inflammation (Gertsch 2008), as described above in the review. We also expect CBN to have effect on PTSD induced neuroinflammatory changes in the brain.

We also observed in the review that both cannabidiol and cannabinol have different mechanism of action, it is therefore possible to combine the two cannabinoids to have a synergistic action in the management of PTSD. The polypharmacy if well tolerated may be novel in the management of PTSD. We will therefore compare the efficacy of this combination with an SSRI sertraline in the management of PTSD. We chose sertraline despite the Cochrane study mentioned above because a clinical trial claimed it is effective in the treatment of PTSD (Davison et al 2002). It will also be necessary to have a placebo control in this type of study.

HYPOTHESES

1. Null hypothesis: There will be no difference in the effectiveness of cannabidiol and cannabinol combination therapy, compared with sertraline in the treatment of the symptoms of PTSD.
2. Alternative hypothesis: There will be a significant difference (i.e. a better outcome) for patients on cannabidiol and cannabinol combination therapy compared with sertraline in the treatment of the symptoms of PTSD.
3. Null hypothesis: There will be no difference in the side effect profile of cannabidiol and cannabinol combination therapy, compared with sertraline in the treatment of the symptoms of PTSD.
4. Alternative hypothesis: There will be a significant difference in side effect profile of patients on cannabidiol and cannabinol combination therapy compared with sertraline in the treatment of the symptoms of PTSD.
5. Null hypothesis: There will be no difference in the effectiveness of cannabidiol and cannabinol combination therapy, compared with placebo in the treatment of the symptoms of PTSD.
6. Alternative hypothesis: There will be a significant difference (i.e. a better outcome) for patients on cannabidiol and cannabinol combination therapy compared with placebo in the treatment of the symptoms of PTSD.
7. Null hypothesis: There will be no difference in the side effect profile of cannabidiol and cannabinol combination therapy, compared with placebo in the treatment of the symptoms of PTSD.
8. Alternative hypothesis: There will be a significant difference in side-effect profile of patients on cannabidiol and cannabinol combination therapy compared with placebo in the treatment of the symptoms of PTSD.

**Proof of Concept**

A double- blind placebo-controlled study will be carried out in a group of patients with PTSD. The study sites will be the Federal Neuropsychiatric Hospital, Yaba Lagos, Nigeria and the 68 Nigerian Army Reference Hospital, Yaba, Lagos Nigeria.

*Aim and Objectives*

The overall aim of this proof-of-concept clinical trial is to investigate the effectiveness of cannabidiol and cannabinol combination therapy in the management of patients with PTSD.

The specific objectives include:

Evaluation of the effectiveness of and cannabinol combination therapy in the treatment in the treatment of specific symptoms of PTSD.

Evaluation of side effects of cannabidiol and cannabinol combination therapy in the treatment of specific symptoms of PTSD.

Comparison of the effectiveness of cannabidiol and cannabinol combination therapy and sertraline in the treatment of specific symptoms of PTSD.

Comparison of the side-effects of cannabidiol and cannabinol combination therapy and sertraline in the treatment of specific symptoms of PTSD.

**METHODS**

*Description of trial design including allocation ratio*

The study design will be a double-blind controlled study. There will be three arms: PTSD patients on cannabidiol and cannabinol combination therapy, PTSD patients on sertraline and PTSD patients on placebo. The allocation ratio to these arms will be 1:1:1.

The design will be parallel in nature with the subjects remaining on the treatment to which they are randomly assigned, as long as they continue in the trial. Both patients and the outcome assessors will be unaware of the treatment assignment. All study patients will be treated for a period of ?8 weeks.

The dose of the Cannabidiol will be 4mg/kg/day which will approximate to 300mg/day for a 70kg patient. Mechoulam and Carlini in 1978 used 200mg/day, Cunha et al in 1980 used 200-300mg/day. The dose of cannabinol will be 40mg/day (Holister and Gillespie 1975).

Patients will be analysed within the group to which they were allocated, irrespective of whether they experienced the intended intervention.

*Eligibility criteria for participants*

Participants will be adults between the age of 18 and 60years with current diagnosis of PTSD (meeting the ICD-10 criteria).

*Inclusion criteria:*

* Adults who are above 18 years of age and gave informed consent
* Currently meet the DSM-5 diagnosis of PTSD and confirmed with the MINI-PLUS

Exclusion criteria:

* Any other diagnosis meeting the ICD-10/DSM 5 criteria except the other stress related disorders, depression and substance use disorder.

• Having an DSM-5 diagnosis of an organic mental illness such as a seizure disorder or severe brain injury

• Serious or chronic physical illness

• Known severe drug allergies or hypersensitivity to cannabidiol or cannabinol.

Treatment Setting

The study will be carried out at the Federal Neuro-Psychiatric Hospital (FNPH) Yaba, Lagos and the 68, Nigerian Army Reference Hospital using the out-patient clinics population.

Ethical clearance will be obtained from the ethical committee of the Federal Neuropsychiatry Hospital, Yaba, Lagos and the 68, Nigerian Army Reference Hospital, Yaba, Lagos. Approval will be sought from the regulatory authority in Nigeria. The National Agency for Food and Drug Administration and Control (NAFDAC) before the medication is brought into the country and use in the trials.

*Procedures*

*Investigators meeting*: Investigators will consist of psychiatrists, senior registers and pharmacists at the designated centers. A meeting of the investigating team will be called to discuss the study methodology in detail and train investigators on instruments we intend to use in the study. Another meeting will be called to carry out inter-rater reliability assessments on the instruments to be used to assess the various parameters we want to measure. We will assign roles to different investigators at this meeting with emphasis on separating who undertakes patient’s recruitment, interventions and outcome measures from one another in order to limit study bias. There is also the need to have a conference to publicize the trials and explain the study to the staff of the two hospitals.

*Recruitment:* All patients seen at the outpatient unit of the two hospitals who meet the inclusion criteria for the study shall be given the opportunity to participate in the study. However only consenting patients who meet the inclusion criteria will be recruited and simple random sampling will be used to assign the participants to different study arms of the clinical trial.

*Baseline assessment*: Study procedures will be explained to potential participants with diagnosis of PTSD as confirmed by the psychiatrists and written informed consent will be obtained from each participant. A questionnaire will be used to collect biographic and socio-economic information. The Mini-International Neuropsychiatric Interview (MINI) will be used to screen the participants for any other ICD-10/DSM-V diagnosis. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2013) which is the gold standard for PTSD will be used to confirm diagnosis and assess symptoms of PTSD over the past week.

*Type of randomization; details of any restriction (such as blocking and block size)* Randomization sequence into either of the three groups will be generated using the ballot method with a 1:1:1 allocation using random block sizes of between 3 and 9.

*Mechanism for random allocation sequence:* The allocation sequence will be concealed from the researchers enrolling and assessing participants in sequentially numbered sealed envelopes.

*Blinding*

Blinding will be achieved with the use of centralised randomisation, identical packaging of cannabidiol, cannabinol and sertraline and the use of independent outcome assessors (for assessment of efficacy and side effects).

Assessments will be conducted at baseline, 6weeks and at 12 weeks follow up.

Themain outcome measure will be improvement in symptoms of PTSD on CAPS-5. All subjects will be treated for a period of six weeks.

*Secondary outcomes measures:*

* Differences in the efficacy of cannabidiol and cannabinol combination therapy compared to sertraline and placebo.
* Side effects: This will be measured using Glasgow checklist.
* Differences in the side effects of cannabidiol and cannabinol combination therapy compared to sertraline and placebo.
* Acceptability of treatment – number of drop-outs and reasons for dropping out of the trial, and patients’ expressed views regarding the drug treatment. This will be measured with the aid of Morisky Medication Adherence scale (MMAS).

INSTRUMENTS

* Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2013).
* Morisky Medication Adherence scale (MMAS) (Morisky et al.,1986).
* Glasgow Antipsychotics side effects check list (Waddell and Taylor, 2008).
* Biographic and socioeconomic questionnaire.
* The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

**Statistical methods used to compare groups for primary and secondary outcomes**

The primary endpoint will be changes in the severity and numbers of PTSD symptoms as measured by CAPS-5 during the 6 weeks of treatment in intent-to treat sample. Secondary endpoints will be severity of side effects on the Glasgow checklist and the dropout rate in the three groups.

Repeated measures ANOVA will be used in this regard. The proportion of responders and the proportion of patients with moderate to severe side effects will be compared between the treatment groups**.**  Level of significance will be set at p<0.05 and all tests will be 2-sided.

**Sample size determination**

With a non-inferiority trial design, detecting a reduction of at least 15% in symptoms reduction over a period of 6 weeks and with the following assumptions made; a 5% significance level, power of 80% and an anticipated dropout rate of about 20%.

Sample size can be calculated using the formula below.

n = the sample size in each of the groups

μ1 = population mean in treatment Group 1

μ2 = population mean in treatment Group 2

μ1 − μ2 = the difference the investigator wishes to detect 15% in symptoms reduction

σ2 = population variance (SD)

a = conventional multiplier for alpha = 0.05

b = conventional multiplier for power = 0.80

Formula

A sample size of 28 subjects will be needed in each of the three group.

*Withdrawal from study*: Patients will be withdrawn from the study if they retract consent, require a change of medication owing to efficacy or intolerable/serious adverse drug reactions that require a stoppage of or switch in treatment.

*Intervention for each of the arms*.

* *Study arm*: this will include subjects on cannabidiol at 300mg daily and cannabinol at 40mg per day only.
* *Control arm*: this group will include subjects on sertraline at 100mg daily only.
* *Placebo arm*: this group will include subjects on the placebo capsule at 100mg daily

Other medications apart from those for the study will not be permitted during the period, except benzodiazepines where necessary. Adverse effects will be periodically assessed with the Glasgow checklist and reported at each assessment.

*Duration of study*

The entire project will be completed within six months.

**Expected outcomes**

We expect the proposed study to broaden our knowledge of the neuroprotective effects of CBD and the effects of CBN on chronic inflammation.

The effects of CBD and CBN on PTSD will help in determining if CBD and CBN will provide useful data for other stress induced disorders.

The proposed project will make an original contribution to the field of knowledge because it explored a novel option in the management of PTSD. More importantly, the new knowledge may lead to discovering new targets for novel and more effective treatments for PTSD.

**Ethical Considerations**

The protocol will be submitted to the ethical review committee of the Federal Neuropsychiatric Hospital Yaba and the 68, Nigerian Army Reference Hospital, Yaba. Participation in the clinical trial will be completely voluntary and written informed consent will be obtained from all participants prior to the initiation of any study procedures. The consent form and the researchers will explain the outline and nature of the study and procedures. This study will maintain the confidentiality of all subjects by excluding their identifying details, such as their name, address or telephone numbers on the consent forms, biographical forms and other data capture sheets. Anonymity will be maintained by de-identifying collected data - each participant will be identifiable only by a unique identifier code.

There will be no incentives for participation. However, participants will be reimbursed for travel costs at each visit at a rate of five hundred naira per visit. All participants have the right to withdraw from the research study at any time, without disadvantage. Participants may only request feedback on their questionnaires and tests indirectly once the study is completed. This will take the form of the completed research report, which will provide an overview of scores and results, rather than particular results of individual participants.

No adverse effects due to the administration of the questionnaires and tests selected in this study or the greater research project are expected although it is possible that some participants may become distressed by the nature of information requested in the measuring instruments to be used. However, follow up telephone numbers for available clinical services will be made available to participants at the time of consent and after completing the questionnaires and tests. Patients who experience distress or other symptoms related to the medications being tested will be treated freely at a registered hospital.

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