Targeting the endocannabinoid system for management of HIV-associated neuropathic pain: A systematic review

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A R T I C L E   I N F O

A B S T R A C T

Human immunodeficiency virus (HIV) infection and antiretroviral therapy can independently induce HIV-associated neuropathic pain (HIV-NP). There is a dearth of drugs or therapeutic modalities that can alleviate HIV-NP. Smoked cannabis has been reported to improve pain measures in patients with neuropathic pain. Cannabis, phytocannabinoids, and the endocannabinoids such N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG), produce some of their effects via cannabinoid receptors (CBRs). Endo-cannabinoids are degraded by various enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase. We searched PubMed, Google Scholar, clinicaltrials.gov and clinicaltrialsregister.eu using various key words and their combinations for published papers that studied HIV-NP and cannabis, cannabinoids, or endo-cannabinoids up to 27th December 2020. All original research articles that evaluated the efficacy of molecules that modulate the endocannabinoid system (ECS) for the prevention and/or treatment of pain in HIV-NP animal models and patients with HIV-NP were included. The PubMed search produced a total of 117 articles, whereas the Google Scholar search produced a total of 9467 articles. Amongst the 13 articles that fulfilled the inclusion criteria 11 articles were found in both searches whereas 2 articles were found in Google Scholar only. The clinicaltrials.gov and clinicaltrialsregister.eu searches produced five registered trials of which three were completed and with results. Ten preclinical studies found that the endocannabinoids (2-AG and AEA), synthetic mixed CB1R/CB2R agonist WIN 55,212-2, a CB2R-selective phytocannabinoid β-caryophyllene, synthetic CB2R-selective agonists (AM1710, JWH015, JWH133 and Gp1a, but not HU308); FAAH inhibitors (palmitoylallyla-mide, URB597 and PF-3845) and a drug combination of indomethacin plus minocycline, which produces its effects in a CBR-dependent manner, either prevented the development of and/or attenuated established HIV-NP. Two clinical trials demonstrated greater efficacy of smoked cannabis over placebo in alleviating HIV-NP, whereas another clinical trial demonstrated that cannabidivarin, a cannabinoid that does not activate CBRs, did not reduce HIV-NP. The available preclinical results suggest that targeting the ECS for prevention and treatment of HIV-NP is a plausible therapeutic option. Clinical evidence shows that smoked cannabis alleviates HIV-NP. Further research is needed to find out if non-psychoactive drugs that target the ECS and are delivered by other routes than smoking could be useful as treatment options for HIV-NP.

1. Introduction

Neurological complications are common in human immunodeficiency virus (HIV)-infected persons, with a prevalence of 35% among people living with HIV (PLWH) (IASP, 2014–2015). The most prevalent neurological complication affecting PLWH is distal symmetric polyneuropathy (DSP). These neuropathies are either attributed to the virus itself (HIV-distal symmetric polyneuropathy [HIV-DSP]) or they arise as a residual effect of antiretroviral medications, especially the nucleoside reverse transcriptase inhibitors, causing antiretroviral toxic neuropathy, which may be dose-limiting (Cavaletti, 2007). They both have a similar clinical picture such that it is nearly impossible to diagnose the actual causative effect (Kaku and Simpson, 2014). Clinically, HIV-DSP can be asymptomatic or manifests with both negative and positive signs and symptoms such as decreased or absent ankle jerks, decreased pinprick and vibration sensation in the distal lower extremities, as well as numbness, tingling, pins and needles sensations, burning sensations or pain in a stocking-glove distribution (Schütz and Robinson-Papp, 2013; Verma et al., 2005). Unfortunately, HIV-sensory neuropathy including HIV-associated neuropathic pain (HIV-NP) continues to be a major cause of disability and an unmet medical need as there are no current United States of America (USA) Food and Drug Administration (FDA) approved medications (Kaku and Simpson, 2014). The South African Medical Research Council (SAMRC) Alcohol, Tobacco and Other Drug Research Unit identified HIV-NP as a condition to evaluate the effectiveness of cannabinoids because of the high burden of HIV-NP in South Africa and "the absence of empirical evidence supporting the efficacy of pharmacological agents typically recommended for the management of neuropathic pain in this population group" (Augustine et al., 2018). Medications that are regularly used for the treatment of other forms of neuropathic pain are usually used to treat HIV-NP, but unfortunately, they have not been effective in relieving HIV-NP. These include antidepressants, anticonvulsants, topical agents, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (Gonzalez-Duarte et al., 2008). A questionnaire-based study showed that HIV-patients used cannabis for symptom management and reported improvement of symptoms such as nausea, muscle pain, anxiety and HIV-NP after using cannabis (Woolridge et al., 2005). A meta-analysis of randomised clinical trials (RCTs) on the treatments of HIV-NP found out that only smoked cannabis, recombinant human nerve growth factor, and capsaicin 8% transdermal patch were effective in reducing pain (Phillips et al., 2010). The Canadian Pain Society in 2014 moved cannabinoids from being a fourth-line to a third-line treatment option for chronic neuropathic pain and they considered the evidence from HIV-NP, diabetic neuropathy, posttraumatic or postsurgical neuropathic pain, and mixed central and peripheral neuropathic pain (PNP) studies to be some of the strongest for making that decision (Moulin et al., 2014; Mu et al., 2017). The European Pain Federation panel expert also published an opinion that medical cannabis and cannabis-based medicines can be considered as third-line therapies for chronic neuropathic pain (Häuser et al., 2018).

For thousands of years, *Cannabis sativa* has been used for medicinal purposes including pain management (Hill et al., 2017; Pain, 2015; Touw, 1981; Zlas et al., 1993). The discovery of the phytocannabinoid delta-9-tetrahydrocannabinol (delta-9-THC; Gaoni and Mechoulam, 1964, Rahn and Hohmann, 2009) put cannabis back on the map as a treatment option for different types of pain. Delta-9-tetrahydrocannabinol binds to two G protein-coupled receptors (GPCRs) cannabinoid type 1 receptor (CB1R) and cannabinoid type 2 receptor (CB2R), which were discovered in the nineties (Matsuda et al., 1990; Munro et al., 1993; Rahn and Hohmann, 2009). The CB1Rs are predominantly (but not exclusively) expressed in the central nervous system (CNS) in areas responsible for pain processing. Previously, CB2Rs were thought to be only expressed in non-neuronal immune cells and referred to as the "the peripheral CB receptor (CBR)" (Munro et al., 1993; Zou and Kumar, 2018). Later, CB2R expression was discovered in the brain (Onaivi et al., 2006; Van Sickle et al., 2005), microglia (Núñez et al., 2004) and in brain areas responsible for nociceptive integration (Fine and Rosenfeld, 2013). The endocannabinoid system (ECS) consists of the CBRs (Matsuda et al., 1990; Munro et al., 1993) and their most studied endogenous ligands N-arachidonoylethanolamine (anandamide, AEA) (Devane et al., 1992) and 2-arachidonoylglycerol (2-AG) (Sugiura et al., 1995) discovered in the early nineties, the enzymes involved in the synthesis and degradation of the endocannabinoids, and the endocannabinoid membrane transporters (Fig. 1). The endocannabinoids are produced from phospholipid precursors that come from the cell membrane. The endocannabinoid AEA is mainly synthesised from *N*-acyl-phosphatidylethanolamine (NAPE) by the enzymatic action of NAPE-specific phospholipase D (NAPE-PLD) (Basavarajappa, 2007; Di Marzo et al., 1994). While 2-AG is mainly synthesised from α or β diacylglycerol (DAG) by the catalytic action of DAG lipase (DAGL) (Basavarajappa, 2007; Prescott and Majerus, 1983; Sugiura et al., 1995). The endocannabinoids are synthesised on-demand and changes that affect the activity of enzymes involved in either synthesis or degradation will have significant effects on their availability (Munawar et al., 2017). They also act in a retrograde fashion as they are released from the postsynaptic terminal to act on the presynaptic terminal (Fig. 1) (Castillo et al., 2012). The degradation or inactivation of AEA is mainly catalysed by fatty acid amide hydrolase (FAAH) which breaks it into arachidonic acid and ethanolamine (Basavarajappa, 2007; Cravatt et al., 1996). While the degradation of 2-AG is mainly catalysed by monoacylglycerol lipase (MAGL) which breaks it into arachidonic acid and glycerol (Basavarajappa, 2007; Dinh et al., 2002; Zou and Kumar, 2018). Besides FAAH and MAGL, the endocannabinoids are inactivated by other enzymes such as serine hydrolase α-β-hydrolase domain-containing 6 (ABHD6), serine hydrolase α-β-hydrolase domain-containing 12 (ABHD12), cyclooxygenases (COXs) and lipoxygenases (LOXs) (Maccarrone, 2017; Murataeva et al., 2014; Rouzer and Marnett, 2011).

Besides the phytocannabinoids and the endocannabinoids, there are synthetic cannabinoids that have been produced based on sharing structure similarities of the phytocannabinoids and hence can activate the CBRs (Zou and Kumar, 2018).

The use of cannabis, also known as marijuana, is illegal in most parts of the world due to the associated psychotic side effects and altered mental status. However, the number of countries that have decriminalised and legalised the use of cannabis for recreational use, medicinal use or both is increasing (Bonny-Noach and Sagiv-Alayoff, 2019; Putri, 2020). Countries where medical use of cannabis is legal at either national/federal level or at various state levels include Argentina, Australia, Austria, Belgium Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Finland, Germany, Ghana, Greece, Israel, Italy, Jamaica, Lesotho, Luxembourg, Malawi, Malta, the Netherlands, North Macedonia, Mexico, Norway, Peru, Poland, Portugal, Romania, San Marino, South Africa, Switzerland, Turkey, the United Kingdom, Uruguay, USA, Zambia and Zimbabwe (Bonny-Noach and Sagiv-Alayoff, 2019; Fragoso et al., 2020; Putri, 2020; Wright, 2019). Cannabis can produce antinociceptive effects and psychoactive effects through the activation of CB1R (Fine and Rosenfeld, 2013). On the other hand, activation of CB2R can produce antinociceptive effects without the psychosis associated with CB1R activation (Fidyt et al., 2016). In addition to the psychoactive side effects, smoked cannabis has an additional side effect related to the carcinogenicity associated with smoking as a delivery route (Taylor and Hall, 2003). Thus, there is a need to explore other molecules that target different parts of the ECS and possible different delivery routes.

The aim of this systematic review was to evaluate the potential of targeting the ECS for prevention and treatment of HIV-NP using information from published articles on preclinical studies and clinical trials of HIV-NP.
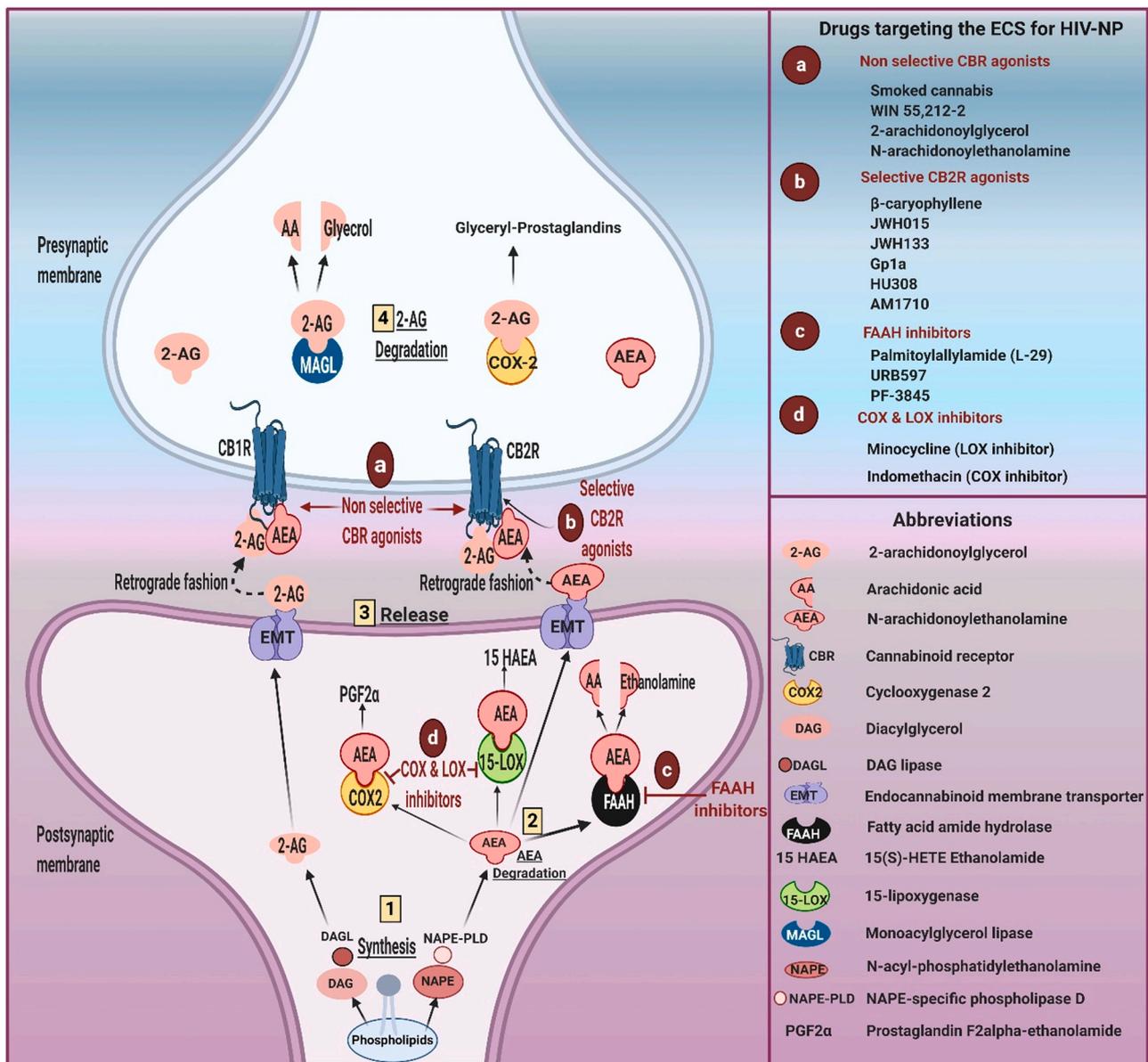
Fig. 1. Schematic diagram of the endocannabinoid system (ECS) and the targets of drugs evaluated in preclinical studies and clinical trials of human immunodeficiency virus-associated neuropathic pain (HIV-NP). The endocannabinoids 2-AG and AEA are produced from phospholipid precursors. 1]- AEA is mainly synthesised from NAPE by the enzymatic action of NAPE-PLD. While 2-AG is mainly synthesised from α or β DAG by the catalytic action of DAGL. 2]- The degradation of AEA is mainly catalysed by FAAH which breaks it into AA and ethanolamine and occurs mainly in the postsynaptic terminal. 3]- The endocannabinoids are released in a retrograde fashion and transported by EMTs from the postsynaptic terminal to act on CBRs on the presynaptic terminal. 4]-In the presynaptic terminal, the degradation of 2-AG is mainly catalysed by MAGL which breaks it into AA and glycerol. The endocannabinoids are also inactivated by other enzymes such as COX and LOX. The drugs that were used to alleviate HIV-NP in preclinical studies and clinical trials and target the ECS can be classified as a) non-selective CBR agonists, b) selective CB2R agonists, c) FAAH inhibitors and d) COX and LOX inhibitors. Figure created by the authors using BioRender.com.

2. Methods

2.1. Literature search

The U.S. National Library of Medicine, Washington, DC (MEDLINE-PubMed) and Google Scholar were used to search for articles for this study up to 27th December 2020. The following keywords or phrases "HIV", "antiretroviral", "neuropathic pain", "painful neuropathy", "cannabis", "cannabinoid" and "endocannabinoid" were proposed and searched for in PubMed and Google Scholar. Twelve searches were done using different combinations of the keywords or phrases ("HIV" OR "antiretroviral") AND ("neuropathic pain" OR "painful neuropathy") AND ("cannabis" OR "cannabinoid" OR "endocannabinoid"). The same

keywords were used to search for clinical trials registered on clinicaltrials.gov and clinicaltrialsregister.eu, up to 27th December 2020. Searches including the combination of the above keywords and Africa were also done on PubMed and Google Scholar up to 27th December 2020, taking into consideration that the continent has the highest number of PLWH (about 70% of the world population of PLWH) (Shiau et al., 2020) and possibly HIV-NP.

2.2. Inclusion and exclusion criteria for the articles

Primary research articles that reported the evaluation of the efficacy of molecules that modulate the ECS for the prevention and/or treatment of HIV-NP in preclinical studies or clinical trials were included. Clinical

trials registered on clinicaltrials.gov and clinicaltrialsregister.eu, evaluating the effect of cannabis/cannabinoids on HIV-NP were also included. The following articles were excluded: articles written in a language that is not English, reviews, book chapters, theses, news articles, posters, commentaries, in vitro studies, preclinical studies that used animal models but did not evaluate the effects of drugs, retrospective chart reviews, questionnaire-based studies and other irrelevant articles.

3. Results

The PubMed searches produced 117 articles which were reduced to 44 articles after the removal of duplicates. Thirty-three articles were excluded for various reasons detailed in Supplemental Table 1 and Supplemental Fig. 1, which shows the study flow information. Thus, 11 articles from PubMed searches fitted the inclusion criteria. The Google Scholar searches produced 9467 articles, after discarding articles that did not fit the inclusion criteria, only 13 articles fitted the inclusion criteria. Of these, 11 were similar to the PubMed searches, thus, two extra articles were found in Google Scholar. The clinicaltrials.gov and clinicaltrialsregister.eu searches produced five registered trials of which three were completed and with results, these three were already found in the the PubMed and Google Scholar searches. Thirteen articles that fulfilled the inclusion criteria were included in this review, analysed, and discussed in detail below. These 13 articles included 10 preclinical studies and 3 clinical trials. While the PubMed searches including the keyword Africa and the other keyword combinations did not produce any articles, a Google Scholar search produced many articles which did not fit the inclusion criteria, of which some articles were included in the discussion about what has been done in the continent with regard to HIV-NP and cannabis/cannabinoids/endocannabinoids.

3.1. Preclinical studies

Ten preclinical studies evaluated the effects of endocannabinoids, cannabinoids, FAAH inhibitors and the indomethacin plus minocycline (IPM) combination (Table 1). The antiretroviral drug 2′-3′-dideoxycytidine (zalcitabine, ddC) was used to induce HIV-NP in 4 studies, the antiretroviral drug stavudine in one study, HIV-glycoprotein 120 (HIV-gp120) in three studies, one study used HIV-gp120 + ddC, and the last study used LP-BM5 murine retrovirus. The drugs evaluated in the eight studies can be classified under four categories: non-selective CB1R/CB2R agonists, selective CB2R agonists, FAAH inhibitors and COX and LOX inhibitors (IPM combination).

3.1.1. Non-selective CB1R/CB2R agonists

The synthetic non-selective CB1R/CB2R agonist WIN 55,212-2 alleviated mechanical sensitivity induced by ddC, stavudine, HIV-gp120 or HIV-gp120 + ddC (Huang et al., 2013; Wallace et al., 2007a, 2007b). The administration of HIV-gp120 + ddC produced significantly more mechanical hypersensitivity than either ddC or HIV-gp120 alone, and WIN 55,212-2 alleviated the ddC-induced mechanical hypersensitivity more efficaciously than that induced by HIV-gp120 + ddC (Wallace et al., 2007b). Recently, HIV-gp120 has been shown to reduce the analgesic effects of WIN 55,212-2 (Palma et al., 2018). Thus, although cannabinoids alleviate hypersensitivity due to HIV-NP, the interaction with HIV-gp120 might reduce their effectiveness. The endocannabinoids

Table 1
Preclinical studies on the effects of drugs that target the endocannabinoid system on HIV-NP.

HIV-NP model		Molecule	Drug Class	Effects	Effects of CBR antagonists on the activity of the compound	Reference
Agents used to induce NP	Animal					
HIV-gp120	Male Wistar rats	WIN	Synthetic non-selective CB1R/CB2R agonist	Reversed established mechanical hypersensitivity	No antagonists were used	Wallace et al. (2007a)
ddC alone, HIV-gp120 + ddC	Male Wistar rats	WIN	Synthetic non-selective CB1R/CB2R agonist	Completely reversed established mechanical hypersensitivity associated with ddC treatment. Partially reversed mechanical hypersensitivity associated with gp120 + ddC treatment	No antagonists were used	Wallace et al. (2007b)
ddC	Male Wistar rats	L-29	FAAH inhibitor	Reversed established mechanical hypersensitivity	CB1R antagonist SR141716a and CB2R antagonist SR144528 antagonised	Wallace et al. (2007c)
HIV-gp120	Male SD rats	AM1710	Synthetic CB2R-selective agonist	Prevented the development of mechanical hypersensitivity	No antagonists were used	Wilkerson et al. (2012)
Stavudine	Male Wistar rats	WIN	Synthetic non-selective CB1R/CB2R agonist	Completely reversed established mechanical hypersensitivity	No antagonists were used	Huang et al. (2013)
HIV-gp120	Male SD rats	URB597 and PF-3845	FAAH inhibitors	Reduced cold and tactile/mechanical allodynia with limited effects on mechanical hyperalgesia	CB1R antagonist AM251 and CB2R antagonist SR144528 antagonised	Nasirinezhad et al. (2015)
ddC	Female BALB/c mice	2-AG and AEA	Endocannabinoids, non-selective CB1R/CB2R agonists	Reversed established thermal hyperalgesia	CB1R antagonist AM251 and CB2R antagonist AM630 antagonised	Munawar et al. (2017)
ddC	Female BALB/c mice	BCP	CB2R-selective phytocannabinoid	Prevented the development of mechanical allodynia. Reversed established mechanical allodynia	CB2R antagonist AM630, but not the CB1R antagonist AM251, antagonised	Aly et al. (2019)
ddC	Female BALB/c mice	IPM combination	Indomethacin is a NSAID. Minocycline is a semi-synthetic tetracycline antibiotic	Reversed established thermal hyperalgesia and mechanical allodynia	CB1R antagonist AM251 and CB2R antagonist AM630 antagonised	Masocha and Thomas (2019)
LP-BM5 murine retrovirus	Female C57BL/6 mice	JWH015, JWH133, Gp1a, and HU308	Synthetic CB2R-selective agonists	All the CB2R agonists, except HU308, reversed established mechanical allodynia	No antagonists were used	Sheng et al. (2019)

2-AG, 2-arachidonoyl glycerol; AEA, N-arachidonoyl ethanolamine (anandamide); BCP, β-caryophyllene; CBR, cannabinoid receptor; ddC, 2′-3′-dideoxycytidine, zalcitabine; FAAH, fatty acid amide hydrolase; gp, glycoprotein; HIV, human immunodeficiency virus; IPM, indomethacin plus minocycline; L-29, palmitoylallylamide; NSAID, non-steroidal anti-inflammatory drug; SD, Sprague-Dawley; WIN, WIN 55,212-2.

2-AG and AEA, which are non-selective CB1R/CB2R agonists, alleviated thermal hyperalgesia induced by ddC (Munawar et al., 2017). The antihyperalgesic activities of AEA were dependent on both CB1R and CB2R, whereas those of 2-AG were dependent on CB1R but not CB2R (Munawar et al., 2017).

3.1.2. Selective CB2R agonists

A CB2R-selective phytocannabinoid β-caryophyllene (BCP) prevented the development of ddC-induced mechanical allodynia and also alleviated established ddC-induced mechanical allodynia (Aly et al., 2019). The antiallodynic effects of BCP were dependent on CB2R but not CB1R. Prophylactic treatment with BCP also prevented ddC-induced inflammation i.e. blocked the ddC-induced gene expression of proinflammatory cytokines both in the periphery and CNS (Aly et al., 2019). The intrathecal administration of the synthetic CB2R-selective agonist AM1710 prevented the development of mechanical hypersensitivity induced by HIV-gp120 (Wilkerson et al., 2012). The activities of four synthetic CB2R-selective agonists (JWH015, JWH133, Gp1a, and HU308) were evaluated on LP-BM5 murine retrovirus-induced mechanical allodynia (Sheng et al., 2019). The LP-BM5 murine retrovirus induces murine acquired immunodeficiency syndrome (MAIDS) and DSP. Administration of JWH015, JWH133 and Gp1a, but not HU308, alleviated LP-BM5 murine retrovirus-induced mechanical allodynia but did not affect the LP-BM5 murine retrovirus-induced neuroinflammation (Sheng et al., 2019).

3.1.3. FAAH inhibitors

A FAAH inhibitor palmitoylallylamide (L-29) alleviated mechanical sensitivity induced by ddC and its effects were comparable to gabapentin, which is used in the management of NP (Wallace et al., 2007c). The antiallodynic activities of L-29 were dependent on both CB1R and CB2R, but it was devoid of the locomotor side effects associated with CB1R activation (Wallace et al., 2007c). Two other FAAH inhibitors, URB597 and PF-3845, alleviated HIV-gp120-induced cold and tactile/mechanical allodynia with limited effects on mechanical hyperalgesia (Nasirinezhad et al., 2015). Their antiallodynic effects were comparable but lasted longer than that of gabapentin and were dependent on both CB1R and CB2R (Nasirinezhad et al., 2015).

3.1.4. COX and LOX inhibitors

Although indomethacin, a NSAID, and minocycline, a semi-synthetic tetracycline antibiotic, are not cannabinoids, they inhibit COXs and LOXs (Daymond and Rowell, 1988) enzymes, respectively, which are also involved in the inactivation of endocannabinoids (Maccarrone, 2017; Murataeva et al., 2014; Rouzer and Marnett, 2011). A previous study showed that the IPM combination has CB1R-dependent anti-allodynic effects in an animal model of chemotherapy-induced neuropathic pain (CINP) (Parvathy and Masocha, 2015). The IPM combination alleviated both mechanical allodynia and thermal hyperalgesia induced by ddC. The antiallodynic and antihyperalgesic effects of IPM were dependent on both CB1R and CB2R (Masocha and Thomas, 2019). The synthetic non-selective CB1R/CB2R agonist WIN 55,212-2 dose-dependently reduced the time spent on the rotarod, thus induced motor impairment, whereas IPM did not (Masocha and Thomas, 2019).

3.2. Clinical trials

We found five clinical trials registered on clinicaltrials.gov and clinicaltrialsregister.eu on HIV neuropathy and cannabis/cannabinoid/endocannabinoid: three completed trials that have published results (Abrams et al., 2007; Eibach et al., 2020; Ellis et al., 2009), one trial which was withdrawn because of "Withdrawal of pharmaceutical support from Novartis - no participants randomised" (https://clinicaltrials.gov/ct2/show/NCT00723918) and the last one is still recruiting (Table 2). A search in Google Scholar and PubMed only produced the three published clinical trials. Therefore, three randomised, double-blind, placebo-controlled trials that evaluated the effectiveness of cannabis or cannabinoids on HIV-NP were analysed (Table 3). Two studies examined the effects of smoked cannabis (Abrams et al., 2007; Ellis et al., 2009), while the third and most recent study examined the effects of a cannabinoid, cannabidivarin (CBDV) taken orally in a solution (Eibach et al., 2020). The design of the study by Abrams et al. was parallel placebo-controlled, while those of Ellis et al. and Eibach et al. were crossover placebo-controlled.

Smoked cannabis significantly reduced pain of subjects with HIV-NP in both studies (Abrams et al., 2007; Ellis et al., 2009). On the other hand, CBDV had no significant effects on pain intensity of HIV-NP subjects and its effects were not different from placebo (Eibach et al.,

Table 2
Clinical trials, registered on clinicaltrials.gov and clinicaltrialsregister.eu, evaluating the effects of cannabis/cannabinoids on painful HIV neuropathy.

ClinicalTrials.gov Identifier or EudraCT number	Recruitment status	Date first posted or start date	Study title	Condition	Interventions	Results published
NCT00046722	Completed	October 3, 2002	Marijuana for HIV-related peripheral neuropathy	Peripheral nervous system diseases HIV Infections	Drug: smoked marijuana	Yes Abrams et al. (2007)
NCT00255580	Completed	November 21, 2005	Medicinal cannabis for painful HIV neuropathy	Neuropathic pain	Drug: smoked cannabis	Yes Ellis et al. (2009)
NCT00723918	Withdrawn (withdrawal of pharmaceutical support from Novartis - no participants randomised)	July 29, 2008	Combination of an investigational cannabinoid and methadone for HIV-associated neuropathy	HIV-associated neuropathy Polyneuropathy	Drug: SAB378 Drug: methadone Drug: SAB placebo Drug: methadone placebo	No
2014-005344-17	Completed	August 21, 2015	Oral cannabidivarin (CBDV) solution for treatment of HIV-associated neuropathic pain – a randomised, double-blind, placebo-controlled phase II study.	Chronic painful HIV-associated neuropathy	Drugs: cannabidivarin	Yes Eibach et al. (2020)
NCT03099005	Recruiting	April 4, 2017	Effect of cannabis and endocannabinoids on HIV neuropathic pain	Cannabis HIV neuropathy Pain syndrome	Drug: cannabis	No

Table 3
Randomised, double-blind, placebo-controlled trials on the effectiveness of cannabis or cannabinoids on HIV-NP.

Study drug	Design, dose, and duration of exposure to drug	Number of participants recruited (completed)	Primary Outcome measure	Outcome and conclusion	Adverse events	Reference
Smoked cannabis	Parallel 3.56% delta-9-THC One cigarette TID for 5 days	54 (50) 27 (25) smoked cannabis 27 (25) smoked placebo	Percentage achieving > 30% reduction in pain intensity using the VAS	Cannabis was superior to placebo and significantly reduced neuropathic pain	Mean side effects were low in both groups. However, cannabis group experienced anxiety, sedation, disorientation, confusion, and dizziness significantly more than placebo	Abrams et al. (2007)
Smoked cannabis	Crossover 1–8% delta-9-THC QID for 5 days, 2 weeks washout, crossover to another 5 days of treatment	34 (28)	Change in pain intensity measured by DDS	Cannabis was superior to placebo and significantly reduced neuropathic pain	Dose- and treatment-limiting AEs occurred in two subjects after taking cannabis, one experienced psychosis and another experienced intractable cough Nontreatment-limiting AEs were greater for cannabis than placebo. These were concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst.	Ellis et al. (2009)
CBDV (given orally)	Crossover 400 mg QD for 4 weeks, 3 weeks washout crossover to another 4 weeks of treatment	34, but 2 had missing data (28) 4 dropped out during the study but were included in analysis	Pain intensity on NRS (0–10)	Pain intensity with CBDV was not significantly different to placebo, 0.62 points higher compared to placebo	Incidence of AEs were similar between CBDV and placebo treatments Treatment limiting AE (cough) occurred in one subject during CBDV treatment	Eibach et al. (2020)

CBDV, cannabidivarin; delta-9-THC, delta-9-tetrahydrocannabinol; DDS, Descriptor Differential Scale; HIV-NP, human immunodeficiency virus-associated neuropathic pain; NRS, Numerical Rating Scale; QID, four times daily; QD, once daily; TID, three times daily; VAS, Visual Analogue Scale.

2020). In the study by Abrams et al., the cannabis group smoked one cannabis cigarette three times a day for 5 days. Each cigarette had 3.56% delta-9-THC, whereas the cigarettes for the placebo group had 0% delta-9-THC. Cannabis reduced daily pain by 34% compared to 17% with placebo. In the cannabis group, 52% reported > 30% reduction in pain, whereas in the placebo group, 24% reported > 30% reduction in pain. Thus, cannabis was superior to placebo (Abrams et al., 2007). In the study by Ellis et al. the subjects smoked cannabis four times a day for 5 days and the dose was titrated to 1–8% delta-9-THC and the placebo group smoked cigarettes which had cannabinoids removed. Pain relief was greater with cannabis than placebo with a median difference in Descriptor Differential Scale (DDS) pain intensity change of 3.3 points. The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 and 0.18, respectively. Thus, cannabis was also superior to placebo (Ellis et al., 2009).

In terms of adverse effects (AEs), the cannabis group had more AEs than placebo (Abrams et al., 2007; Ellis et al., 2009), whereas CBDV had AEs like placebo (Eibach et al., 2020). In the study by Abrams et al., the mean side effects scores were low in both cannabis and placebo groups. There were no dropouts because of AEs. However, the cannabis group experienced anxiety, sedation, disorientation, confusion, and dizziness significantly more than placebo (Abrams et al., 2007). In the study by Ellis et al., two subjects dropped out because of cannabis-related AEs; one because of psychosis and another because of intractable cough. Nontreatment-limiting AEs were greater for cannabis than placebo. These were concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst (Ellis et al., 2009). Incidences of AEs were considered similar between CBDV and placebo treatments, however, one subject dropped out because of cough during CBDV treatment (Eibach et al., 2020).

4. Discussion

In this systematic review, three RCTs that evaluated the effects of cannabis and a cannabinoid on subjects with HIV-NP were found and analysed. In addition, ten preclinical studies that evaluated the effects of various drugs that modulate the ECS (Fig. 1) in animal models of HIV-NP were found and analysed.

4.1. Clinical trials on the use of cannabis/cannabinoids for managing HIV-NP

Smoked cannabis significantly reduced pain intensity in two RCTs and was superior to placebo (Abrams et al., 2007; Ellis et al., 2009), whereas the only cannabinoid examined, CBDV, had no significant effects on pain intensity of HIV-NP subjects and its effects were not different from placebo (Eibach et al., 2020). Cannabidivarin is a non-psychoactive cannabinoid found in cannabis, which is structurally similar to cannabidiol and has anticonvulsant activity (Hill et al., 2012). It has low affinity for CB1R and CB2R and produces its effects by acting on various other receptors and enzymes such as transient receptor potential ankyrin 1 (TRPA1), transient receptor potential vanilloid 1 (TRPV1), TRPV2, DAGL-α, etc., (Alves et al., 2020). Although CBDV was found to be safe and have AEs similar to placebo, it showed no promise to be useful for the management of HIV-NP. In one study smoked cannabis did not produce any serious side effects (Abrams et al., 2007), whereas in another study one patient withdrew because of psychosis and another because of intractable cough (Ellis et al., 2009). Some meta-analysis studies suggested that individuals who have taken cannabis have an increased risk of developing psychosis and the risk was greater in those who had more exposure to cannabis in terms of duration and frequency (Marconi et al., 2016; Moore et al., 2007). Beside the psychoactive effects of smoked cannabis, the smoking route of administration is not ideal for treatment of a chronic condition such as HIV-NP. Therefore, cannabinoid formulations that can be administered by other routes could be a better alternative to smoked cannabis. Several

cannabinoid formulations including THC (dronabinol), THC/cannabi-diol (CBD) combination also known as nabiximols (Sativex) and a synthetic cannabinoid that mimics THC (nabilone) have been administered via the oromucosal and oral routes in addition to the inhalation route to evaluate whether they can alleviate various types of neuropathic pain (Aviram and Samuelly-Leichtag, 2017; Mücke et al., 2018; Rabgay et al., 2020; Wong et al., 2020). In a pilot study of 16 patients with CINP, nabiximols oral mucosal spray did not produce significant pain relief compared to placebo, although five out of the 16 patients treated with nabiximols achieved clinically significant pain reduction (Lynch et al., 2014). In a study of 125 patients with PNP, Sativex oral mucosal spray produced significant pain relief compared to placebo (Nurmikko et al., 2007). In another study of 303 PNP patients, Sativex oral mucosal spray produced clinically important improvements in pain (Serpell et al., 2014). An oral formulation of THC was found to alleviate pain due to multiple sclerosis (van Amerongen et al., 2018). Nabilone given orally as an adjuvant was found to improve pain in patients with diabetic PNP (Toth et al., 2012). These studies suggest that cannabinoids administered via the oromucosal or oral route can alleviate neuropathic pain and therefore further research of various cannabinoid formulations administered via the oromucosal and oral route for HIV-NP is warranted.

4.2. Preclinical studies on the effects of cannabis/cannabinoids in HIV-NP animal models

In preclinical studies, non-selective CB1R/CB2R receptor agonists such as WIN 55,212-2 or the endocannabinoids 2-AG and AEA showed antiallodynic and antihyperalgesic activities (Munawar et al., 2017; Wallace et al., 2007a, 2007b). WIN 55,212-2 was more effective against ddC-induced mechanical hypersensitivity compared to mechanical hypersensitivity induced by HIV-gp120 + ddC (Wallace et al., 2007b). Thus, suggesting testing drugs in an animal model which combines both antiretroviral drugs and components of the HIV might be a better and more stringent model for evaluating drugs with potential activity against HIV-NP, which could reduce their failure when evaluated in clinical studies of patients with HIV-NP. This was supported by the fact that HIV-gp120 injected in the periaqueductal grey area diminished the antinociceptive effects produced by the cannabinoid agonist WIN55, 212-2 (Palma et al., 2018). The psychoactive side effects of cannabis and cannabinoids are dependent on the activation of CB1R (Huestis et al., 2001; Mackie and Stella, 2006), therefore non-selective CB1R/CB2R agonists are more likely to produce similar side effects. Thus, CB2R-selective agonists could be a better option as they could produce antiallodynic effects without the unwanted psychoactive effects associated with CB1R activation. Recent preclinical studies have shown that CB2R-selective agonists such as the phytocannabinoid BCP and the synthetic cannabinoids AM1710, JWH015, JWH133 and Gp1a can both prevent the development of mechanical allodynia and reverse established mechanical allodynia in animal models of HIV-NP (Aly et al., 2019; Sheng et al., 2019; Wilkerson et al., 2012). In other models of neuropathic pain, CB2R-selective agonists were reported to have advantages over non-selective CB1R/CB2R agonists because of a favourable therapeutic ratio i.e. sustained efficacy and absence of tolerance, physical withdrawal, or CB1R-mediated side effects (Deng et al., 2015). The placebo-controlled clinical trials that evaluated the efficacy of smoked cannabis are prone to be biased by the ability of the clinical trial subjects to distinguish between cannabis treatment and placebo due to the lack of the psychoactive properties in the latter (Casarett, 2018). This inadequate blinding can result in overestimation of cannabis beneficial effects (Casarett, 2018). Cannabis preparations or extracts that activate only CB2 receptors or lack the psychoactive side effects could overcome this obstacle in blinding.

Endocannabinoids are synthesised on demand and metabolised by enzymes such as FAAH and MAGL (Cravatt et al., 1996; Dinh et al., 2002; Saario et al., 2004). Various FAAH inhibitors such as L-29, URB597 and PF-3845 have been shown to alleviate cold and

tactile/mechanical allodynia induced by either ddc or HIV-gp120 or both (Nasirinezhad et al., 2015; Wallace et al., 2007c). However, no studies that evaluated the effects of MAGL inhibitors on models of HIV-NP were found. In other models of neuropathic pain such as CINP, MAGL inhibitors have been shown to alleviate mechanical allodynia (Guindon et al., 2013; Khasabova et al., 2014; Thomas et al., 2020), thus, evaluating their activities in models of HIV-NP is warranted.

The IPM combination was found to alleviate ddC-induced mechanical allodynia and thermal hyperalgesia in a CBR-dependent manner (Masocha and Thomas, 2019). Preclinical studies have shown that the combination can also alleviate CINP (Masocha and Thomas, 2019; Parvathy and Masocha, 2015). Indomethacin is an NSAID, which inhibits the activity of COX (Daoud et al., 1999; Daymond and Rowell, 1988) and FAAH (Fowler et al., 2003). Minocycline is a semi-synthetic tetracycline antibiotic that has been shown to inhibit the activity of LOX (Chu et al., 2007; Song et al., 2006). The enzymes COX and LOX have been reported to inactivate the endocannabinoids 2-AG and AEA (Alhouayek and Muccioli, 2014; Gatta et al., 2012; Hampson et al., 1995; Kozak et al., 2004; Maccarrone, 2017), thus this combination could increase the availability of endocannabinoids by inhibiting their inactivation. Both drugs are used to manage pain and other clinical conditions such as rheumatoid arthritis (Garrido-Mesa et al., 2013; Nalamachu and Wortmann, 2014), thus it could be easier to evaluate their activity against HIV-NP than other molecules that have not as yet been used clinically.

4.3. Questionnaires on HIV-NP and cannabis use

Although the inclusion criteria were for clinical trials in order to assess the effectiveness of cannabis or cannabinoids on HIV-NP, questionnaire-based articles can give an insight on how cannabis or cannabinoids are used for HIV-NP and the perception of PLWH on how these drugs impact their pain. Cannabis use is common among PLWH and was reported by 26.9% of patients from a representative sample in the USA, 38.5% in Canada and 27% in the United kingdom (Harris et al., 2014; Pacek et al., 2018; Woolridge et al., 2005). A multicentre study of sites in the USA, Africa, and Puerto Rico noticed that PLWH who reported cannabis use for symptom management reside mostly in the USA and no participants from Africa acknowledged cannabis use (Corless et al., 2009). The participants from Africa may not have acknowledged cannabis use because of the illegal nature of cannabis in countries where the study was done at that time. Reasons for cannabis use were recreational followed by medicinal purposes to control symptoms such as lack of appetite, anxiety, stress and pain (Costiniuk et al., 2019). A cohort study that evaluated trends in cannabis use in women with HIV, over a 16 year period, found that the use of cannabis was more common in women with peripheral neuropathy than those with no symptomatic neuropathy (20% vs 15.8%) (D'souza et al., 2012). Corless et al. compared cannabis effect in PLWH to over the counter (OTC) medications on symptoms relief including peripheral neuropathy. While PLWH rated their neuropathy intensity the highest (6.37 / 10) among other symptoms associated with HIV, the use of analgesic medication was rated the lowest (17.8%) (Corless et al., 2009). That indicates the inefficiency of analgesia achieved by available medication in this population. Cannabis was found to be slightly more but not significantly more effective in managing neuropathy than OTC medications (Corless et al., 2009). A questionnaire-based study of PLWH reported significant improvement in tingling, numbness and nerve pain, with cannabis use (Woolridge et al., 2005). Notably, Sohler et. al concluded that cannabis use in PLWH with chronic pain is associated with lower prescription of opioids. This can either mean that cannabis is quite effective in pain reduction in this population or due to the possible misuse potential of opioids, health providers took extra concerns regarding prescribing opioids to patients with a history of using illicit cannabis (Sohler et al., 2018). In contrast, another study reported no association between cannabis use and pain severity or opioid initiation and prescription

([Merlin et al., 2019](#)). Further research is needed to understand whether cannabis can be effective as an alternative to opioids or to decrease opioid use in PLWH or not.

4.4. HIV-NP and cannabis in Africa

Currently, in Africa cannabis is legal for medical use only in a few countries; Ghana, Lesotho, Malawi, South Africa, Zambia and Zimbabwe ([Putri, 2020](#)). The recommendations by the World Health Organization (WHO) to reschedule cannabis and acknowledge its medicinal usefulness could be important for Africa where cannabis is cultivated in a lot of countries and is used for herbal and traditional purposes in various countries such as Mozambique, South Africa and Zimbabwe ([Putri, 2020](#)). In a study done on PLWH in South Africa, it was found that they used cannabis for stress relief and pain relief ([Peltzer et al., 2008](#)). However, a recent study found that a low number of PLWH in South Africa (3%) reported using cannabis for relief of pain ([Wadley et al., 2020](#)). Taking into consideration the available evidence, the dearth of effective pharmacological agents to manage HIV-NP and the needs of PLWH, a SAMRC-supported team of researchers concluded that there was justification for a trial to be conducted in South Africa on the management of HIV-NP using a fixed dose THC: CBD oromucosal cannabinoid spray and was working on a study protocol for such a trial ([Augustine et al., 2018](#)). The information on the use of cannabis to alleviate HIV-NP in Africa is sparse and mainly from South Africa. Thus, there is a need for more studies to understand the use of cannabis in HIV-NP and clinical trials as well.

5. Concluding remarks and opinion

Smoked cannabis has been shown to be effective for managing HIV-NP in two RCTs. However, for clinical management of HIV-NP, which is a chronic condition and needs long term treatment, cannabinoids administered by other routes than smoking and devoid of the psychoactive effects of cannabis would be ideal. The only cannabinoid, CBDV, evaluated in a RCT for managing HIV-NP was found to be safe but not effective to relieve pain, possibly, because of its poor affinity for the CBRs.

Various drugs that target the ECS have been evaluated in preclinical studies of HIV-NP ([Fig. 1](#)). The further development and evaluation of non-selective CB1R/CB2R agonists in clinical studies, even though effective in preclinical studies, might be impeded by the possibility of psychoactive effects linked to CB1R activation. Various CB2R-selective agonists have been found to be effective in preclinical studies and might be worth further evaluation in clinical studies. Of note is the CB2R-selective phytocannabinoid BCP, which is a FDA approved food flavouring agent ([Rahn and Hohmann, 2009](#)). It could be evaluated as an oral nutraceutical for the management of HIV-NP. In addition, the lack of the psychoactive effects would ensure adequate blinding for clinical trials and hence reliable results.

Preclinical models that combine the HIV-gp120 plus antiretroviral drugs may be better models of HIV-NP and hence the drug tested and found effective in the preclinical studies would have a better chance to succeed in clinical trials compared to using animal models that induce neuropathic pain with either the antiretroviral drugs or HIV-gp120 alone.

All the FAAH inhibitors evaluated were effective in preclinical studies of HIV-NP. Various FAAH inhibitors have been tried in clinical trials for various types of pain but to our knowledge, none have progressed so far. No preclinical studies on MAGL inhibitors in models of HIV-NP were found. It might be worth evaluating MAGL inhibitors in animal models of HIV-NP to increase the arsenal of drugs that could be further evaluated in clinical studies of HIV-NP.

The IPM combination is effective in an animal model of HIV-NP and its effects are dependent on CBRs. However, the precise mechanism of action of the IPM combination is not fully known yet. The IPM combination opens a possibility of modulating the ECS with drugs that are already used clinically for other conditions and could be useful for managing HIV-NP.

In conclusion, there is evidence from RCTs for the efficacy of smoked cannabis for alleviating HIV-NP, however, its mode of administration and possible psychoactive side effects makes it not ideal for standard therapy of a chronic condition. Some of the agents that modulate the ECS such as CB2R-selective inhibitors, FAAH inhibitors and the IPM combination were found to be effective in preclinical studies of HIV-NP and might be worth considering for clinical studies. Taking into consideration that more countries are now legalising the medical use of cannabis and the high prevalence of neuropathic pain among PLWH, it is worthy to have reliable data and long-term studies on the efficacy, safety, drug interactions and toxicological effects of cannabis and drugs that modulate the endocannabinoid system in PLWH.

Author contributions

Esraa Aly: Search, extraction and analysis of articles, Writing - original draft; **Willias Masocha:** Conception of the study idea, study protocol design, search, extraction and analysis of articles, Writing - original draft. Both authors read and approved the final manuscript.

Conflicts of Interest

The authors have no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ibneur.2021.01.004](#).

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