

ORIGINAL ARTICLE

Medical cannabis for pain management in patients undergoing chronic hemodialysis: randomized, double-blind, cross-over, feasibility study

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ABSTRACT

Background. Chronic pain is prevalent but difficult to treat in patients undergoing hemodialysis (HD). Effective and safe analgesics are limited in this patient population. Our aim in this feasibility study was to evaluate the safety of sublingual oil based medical cannabis for pain management in patients undergoing HD.

Methods. In a prospective randomized, double-blind, cross-over design, patients undergoing HD with chronic pain were assigned to one of three arms: BOL-DP-o-04-WPE whole-plant extract (WPE), BOL-DP-o-04 cannabinoid extraction (API) or placebo. WPE and API contained trans-delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:6 ratio (1:6, THC:CBD). Patients were treated for 8 weeks, with subsequent 2-week wash out, followed by a cross-over to a different arm. The primary endpoint was safety.

Results. Eighteen patients were recruited and 15 were randomized. Three did not complete drug titration period due to adverse events (AEs) and one patient died during titration due to sepsis (WPE). Of those who completed at least one treatment period, seven patients were in the WPE arm, five in the API and nine receiving placebo. The most common AEs were sleepiness, which improved after dose reduction or patient adaptation. Most AEs were mild to moderate and resolved spontaneously. Serious AEs considered related to study drug included one episode of accidental overdose (WPE) leading to hallucinations. Liver enzymes were stable during cannabis treatment.

Conclusions. Short-term medical cannabis use in patients treated with HD was generally well tolerated. The safety data supports further studies to assess the overall risk-benefit of a treatment paradigm utilizing medical cannabis to control pain in this patient population.

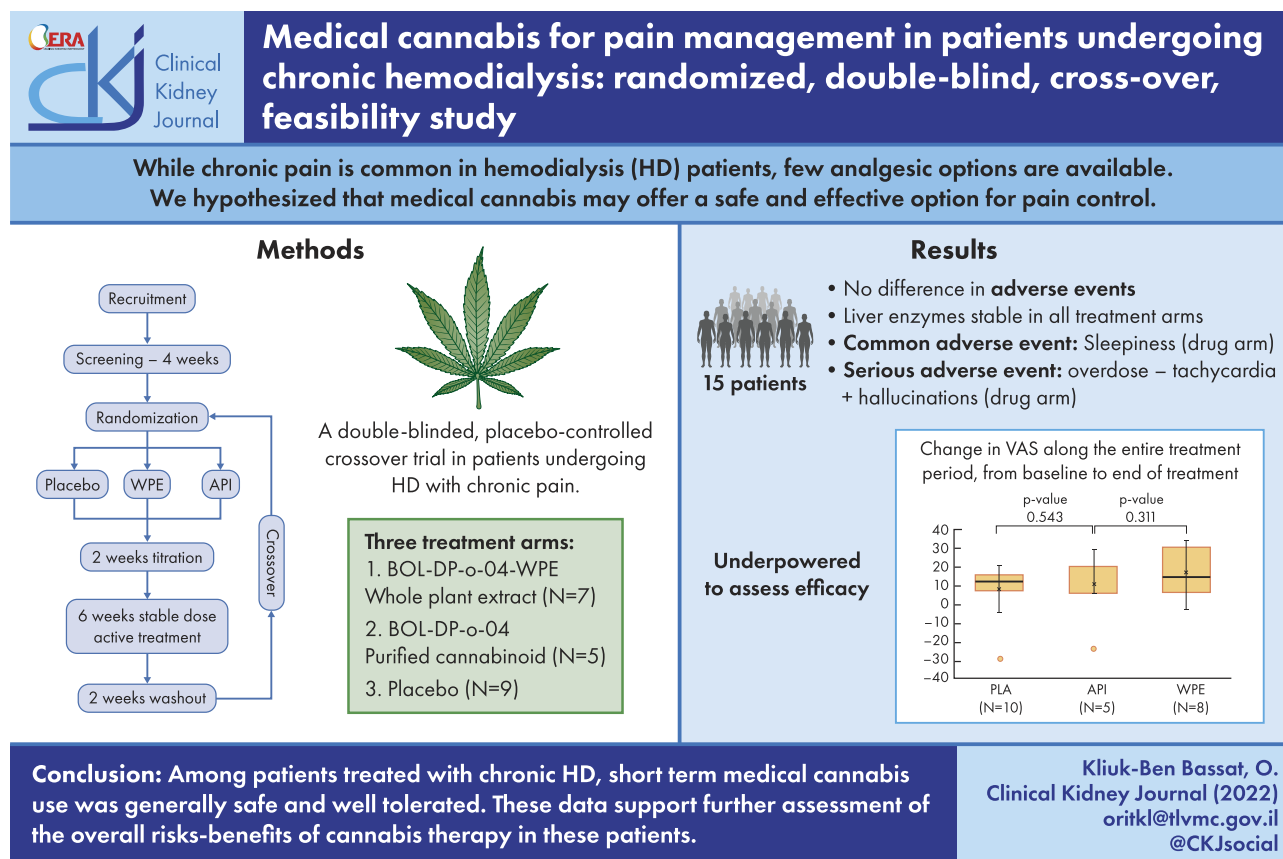
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LAY SUMMARY

Pain management in patients treated with dialysis is challenging, with an unmet need for safer analgesics. The endocannabinoid system is a pharmaceutical target for pain management that could potentially improve additional pain-related symptoms; however, its safety in patients treated with dialysis has not been proven. In the current feasibility study, we conducted a randomized, double-blind, cross-over study to assess the safety of sublingual oil-based cannabis preparation for medical use in hemodialysis patients. The study was comprised of three arms: whole-plant cannabis extract, cannabinoid extraction or placebo. Fifteen patients were randomized. Most adverse events were mild to moderate and resolved spontaneously. Serious adverse event considered related to study drug included one episode of accidental overdose that led to hallucinations. Overall, we demonstrated that a supervised, carefully titrated, short-term medical cannabis use was generally tolerated and was not associated with increased safety signals.

GRAPHICAL ABSTRACT



Keywords: cannabis, end-stage kidney disease, ESKD, hemodialysis, pain

INTRODUCTION

Chronic pain is prevalent in patients undergoing maintenance hemodialysis (HD), with 50%–80% reporting such symptoms [1–4]. Pain is frequently accompanied by sleep disturbances, depression and anxiety, which substantially reduce health-related quality of life [5].

Pain management in patients with end-stage kidney disease (ESKD) is challenging. Similar to the general population, pharmacologic therapies for pain control are usually introduced according to the World Health Organization's "analgesic ladder."

However, in patients with ESKD there is a shortage of approved medications, especially for more severe or nociceptive pain. Under these circumstances, patients are often treated with opioids exposing them to possible side effects such as nausea, anorexia, constipation, fatigue, impaired cognition and risk of addiction [6–8]. Hence, there is an unmet need for safer analgesics to treat patients with ESKD who have significant pain symptoms.

The endocannabinoid system is a promising pharmaceutical target for pain management that could potentially improve additional pain-related symptoms such as loss of appetite or

nausea [9]. Cannabis has two dominant active components: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). When administered concomitantly, CBD potentiates the analgesic effects of THC while reducing its psychotropic effect [10]. There are two pathways of cannabinoid-based drug development: whole-plant extracts can be derived directly from the cannabis plant, which contains an admixture of compounds not necessarily contributing to its desired pharmacological and clinical effects. Alternatively, a single molecule approach can be taken, whereby individual phytocannabinoids (active ingredients are extracted) or novel cannabinoids with therapeutic potential are identified and synthesized, enhancing drug precision [11, 12]. In the general population, cannabis has a moderate effect on pain reduction and is used for various indications. However, data regarding its use in patients undergoing maintenance HD are scarce [13–15].

The aim of this exploratory study was to evaluate the safety of cannabis oil in patients treated with HD, in order to facilitate larger studies and establish the ability of this approach to modulate pain and related symptoms.

MATERIALS AND METHODS

This prospective, randomized, double-blind, three-arm, crossover, feasibility study was conducted at an ambulatory dialysis unit in a large tertiary hospital in Tel-Aviv, Israel. The study protocol was approved by the Hospital's and Israeli Ministry of Health's ethics committees and was performed according to GCP-ICH requirements (study registration number MOH 2018-08-05_003 562).

Study population

Patients treated with maintenance HD who have chronic pain (>3 months) were eligible if their pain persisted despite using conventional analgesic treatment or experienced significant side effects that prompted drug discontinuation. Inclusion criteria included age 30–80 years, pain level ≥ 5 reported by visual analogue scale (VAS) [16], opioids maximal dose below 40 mg/day of morphine (or an equivalent), cannabis abstinence at least 3 months before study enrollment, and the ability and willingness to sign informed consent. Patients were excluded if they had a major psychiatric disorder or past drug/alcohol abuse, a significant cardiovascular disorder (including but not limited to: myocardial infarction within the previous 6 months, congestive heart failure with ejection fraction below 30% or tachycardia), uncontrolled hypertension defined as pre-dialysis blood pressure above 160/100 mmHg, severe central neurological dysfunction or co-administration of drugs interfering with cannabis metabolism. At screening, all patients filled out a Generalized Anxiety Disorder assessment (GAD-7) survey [17]; those with evidence of severe anxiety were excluded from participation and were referred to a psychiatrist's consultation.

Study endpoints

The primary endpoint was safety assessment of cannabis treatment in patients undergoing maintenance HD. These were described using the adverse events (AEs) and serious AE (SAEs) records, and laboratory follow-up, particularly alterations in liver enzymes.

Secondary endpoints included estimated pain reduction using Brief Pain Inventory (BPI) and VAS scores, change in kidney disease-related symptoms assessed by modified Edmonton symptom assessment (ESAS), and change in appetite.

BPI evaluates pain using different scales. It assesses both location and intensity of the pain throughout the last 24 h and its interference in the patient's life [18]. On a scale of 1–10, patients are asked to describe their minimal, maximal and average pain during the 24 h before assessment.

The VAS score, which rates pain intensity, is a sensitive tool for assessing pain and treatment effects [19].

The modified ESAS uses a 0–10 scale to evaluate 10 components: pain, activity, nausea, pruritus, depression, anxiety, drowsiness, appetite, well-being and shortness of breath. A total symptom distress score of 0–100 is calculated [20].

Change in appetite was also assessed, using a designated appetite questionnaire. A score ≤ 14 in this questionnaire was associated with a risk of at least 5% weight loss within 6 months [21].

Study design and conduct

The study design is presented in Fig. 1. The screening period lasted 4 weeks. At the screening visit, patients provided informed consent, and eligibility was determined. Additionally, patients were asked to fill out the GAD-7, VAS, BPI, modified ESAS and appetite questionnaire. During the screening period, patients were assessed weekly for symptoms and modifications in medications. Before randomization, participants were issued a license for cannabis possession and consumption for medical purposes by the ministry of health.

Patients were randomly assigned to one of three arms: whole-plant extract (WPE) arm, purified cannabinoid [active pharmaceutical ingredient (API)] arm or placebo. Each treatment period comprised 2 weeks of titration, followed by 6 weeks of active stable-dose treatment. After completing the first treatment period, patients entered a 2-week washout period, followed by crossing over to a different treatment arm. Each patient was planned to participate in two out of three study arms. Patients were followed for 30 days after the study drug discontinuation of the second treatment arm. Data collection and questionnaires answering schedule are presented in Supplementary data, Table S1.

Study drug

Flowers from *Cannabis sativa* L. (proprietary strain; BOL Pharma, Israel) were dried, ground and decarboxylated at 125°C. The decarboxylated plant material was subjected to CO₂ extraction. The extract was either immediately dissolved in olive oil (BOL-DP-o-04 WPE) or underwent further purification to $\geq 97\%$ pure CBD and THC and then was dissolved in olive oil (BOL-DP-o-04). The final concentrations of CBD and THC in both solutions were 147 mg/mL CBD and 24.5 mg/mL THC. Flavorings were added to all three study drugs (BOL-DP-o-04, BOL-DP-o-04 WPE and placebo) to make taste and scent uniform.

The study drug was given sublingually dissolved in olive oil. The cannabis and placebo were packaged in identical bottles with similar appearance and taste. Both the whole-plant and the purified cannabinoid contained THC and CBD in a 1:6 ratio (1:6 THC:CBD).

Each oil drop contained 0.034 mL, three drops (0.1 mL) contained 2.5 mg THC and 15 mg CBD. First administration was

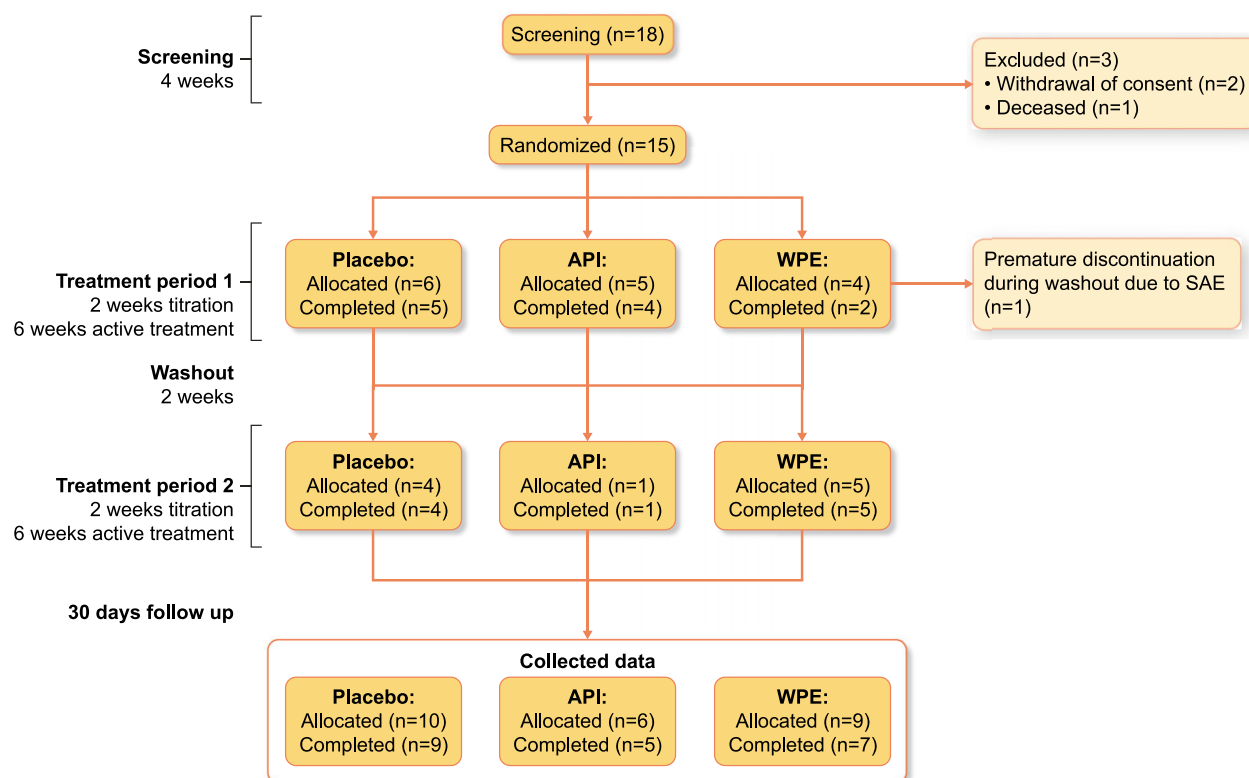


Figure 1: Study design and consort.

given by healthcare providers at the end of a dialysis session, with side effects and vital signs monitoring. The patients remained at the dialysis unit for 2 h to assure they had no immediate side effects or allergic reactions. Thereafter, study drug was taken at home by the patients, according to a titration table provided. All patients were educated on safe drug handling. The titration table is presented in Supplementary data, Table S2. Titration started with three drops once daily, gradually up-titrated according to study protocol to three drops three times per day by the end of the first week. If the patient did not experience side effects, study drug was further increased to a maximal dose of six drops three times daily. In the event that patients experienced side effects, the dose was either unchanged for a longer period or reduced to the previous dose. If analgesic control was achieved according to VAS score, patient remained on the effective dose without further dose escalation. The protocol was amended during the study due to patients' tolerability, after an 80-year-old patient reported weakness and one female patient developed hypotension treated by normal saline following the first dose, and titration started with one drop twice daily. The maximal target dose did not change with the revised titration protocol.

Statistical analysis

Descriptive data is presented as mean [standard deviation (SD)] for normally distributed datasets, and median and interquartile range (IQR) for skewed datasets, as appropriate. Due to its feasibility nature, no formal calculation of sample size was performed, and analyses are presented as descriptive statistics without formal hypothesis testing.

RESULTS

Eighteen patients were recruited between October 2018 to November 2019.

One patient died during the screening period, and two withdrew their consent before randomization. Thus, 15 patients underwent randomization, 13 (86.7%) were males, with mean (SD) age of 64.1 (12.4) (Table 1).

In the first treatment period, five patients were randomized to API, four to WPE and six to placebo. Study drugs were discontinued during titration in one, two and one patients in the API, WPE and the placebo arm, respectively. Two discontinuations were because of patient's preference (one patient on WPE due to sleepiness, one patient on placebo due to constipation). The other two discontinuations were per principle investigator's (PI) decision: in one case of severe sepsis requiring amputation (WPE, considered by the PI as unrelated to study drug) and in another due to significant hypotension (API, considered by PI as related). The hypotensive event led to titration protocol amendment, which was performed after eight titration courses.

During the washout period, one patient was hospitalized due to atrial fibrillation and mitral regurgitation, which led to premature study withdrawal according to the PI's decision. Accordingly, 10 patients started the second treatment period, all of whom completed it and the 30-day follow-up (Fig. 1).

The final analysis included seven patients who completed the WPE arm, five the API arm and nine the placebo arm.

Drug safety

The number of AEs, and the number of patients with an AE were generally similar between treatment arms. There were 24 AE

Table 1: Baseline demographic characteristics of the overall population according to treatment arms.

	All (N = 15)	Placebo (N = 10)	API (N = 6)	WPE (N = 9)
Gender, n (%)				
Female	2 (13.3)	0 (0.0)	2 (33.3)	1 (11.1)
Age (years)				
Median (IQR)	64 (56.5–76.0)	64 (57.0–73.5)	65 (59.5–73.5)	68 (55.0–77.0)
Range	44–80	44–79	44–76	44–80
Height (cm)				
Median (IQR)	170 (166.0–178.0)	176 (170.5–179.75)	171 (161.75–176.5)	170 (166.0–172.0)
Range	158–186	166–186	158–186	160–182
Weight (kg)				
Median (IQR)	75 (69.5–84.45)	81.85 (72.525–86.85)	79.7 (70.0–86.85)	75 (70.0–81.2)
Range	47.0–107.0	69.0–107.0	67.4–99.0	47.0–107.0
BMI (kg/m ²)				
Median (IQR)	24.97 (24.28–28.145)	24.94 (24.43–29.04)	27.38 (25.48–28.33)	24.91 (24.22–28.52)
Range	17.5–36.17	21.82–36.17	24.7–32.33	17.5–36.17
Dialysis vintage (years)				
Median (IQR)	2 (1.0–4.5)	2 (1.0–3.5)	2 (1.25–3.5)	4 (1.0–5.0)
Range	0.5–19.0	1.0–8.0	0.5–5.0	1.0–19.0
Diabetes, n (%)				
Yes	7 (46.7)	5 (50.0)	2 (33.3)	4 (44.4)
Employed, n (%)				
Yes	6 (40.0)	4 (40.0)	2 (33.3)	3 (33.3)

in 8/9 patients (88%) in the WPE arm, 22 events in 6/6 patients (100%) in the API arm, and 19 events in 8/10 patients (80%) in the placebo arm (Table 2). Somnolence and dizziness were the most common AE in the active treatment groups, occurring in five patients in the WPE, three in the API and one in the placebo arm.

Overall, there were 18 SAEs involving seven patients. Four occurred at screening, six in the WPE arm, four in the API arm, three in the placebo arm and one during the follow-up period. Only one SAE was considered by the PI as related to study drug (drug overdose that caused hallucination and tachycardia in the WPE arm).

Two patients died during the study. One patient died during the screening period without receiving any study drug, due to asystole during HD treatment, which was thought to be caused by respiratory distress and hypoxia. Another patient died during the titration period in the WPE arm due to sepsis caused by diabetic septic foot already presented at screening. His death was considered unrelated to the study drug by the PI.

AE/SAE classification by the MedDRA system organ classes are presented in Fig. 2.

Liver enzymes were tested monthly during the study period and remained stable in all treatment arms (Fig. 3).

Pain reduction

At screening, maximal pain assessed by BPI (on 1–10 scale) was 7.4 in WPE, 7.1 in API and 6.9 in placebo. The absolute difference in maximal pain from baseline to end of treatment period (EOT) was –3.3 in WPE, 0.3 in API and –1.3 in placebo. Differences in average pain from EOT to screening were –1.9, 0.6 and –0.9 in WPE, API and placebo, respectively. The differences between treatment arms did not reach statistical significance (Supplementary data, Fig. S1).

Average baseline VAS values were 73.3 for PLA, 77.0 for API and 50.0 for WPE; therefore, they were not comparable between

groups. VAS score from baseline to EOT is presented in Supplementary data, Fig. S2.

Concomitant symptoms

The difference in appetite questionnaire score between baseline and EOT is presented in Supplementary data, Fig. S3.

The mean difference in ESAS score from screening to EOT was –0.35, –1.4 and –0.1 in WPE, API and PLA, respectively, with no significant difference between groups (Fig. 4).

DISCUSSION

In a randomized, double-blind, cross-over study, sublingual oil-based cannabis preparation for medical use was well tolerated and was not associated with a significant increased risk for AE in patients with chronic pain undergoing maintenance HD. Due to the small number of participants, and the study's feasibility nature, efficacy outcomes were described but not compared between groups. To the best of our knowledge, this is the first clinical trial assessing the safety of cannabis use in this population.

Although recreational and medical cannabis is occasionally used in patients treated with HD [3], we are unaware of a prospective study that systematically assessed cannabinoids' safety in this population. Excretion of most cannabinoids occurs via feces, and only 20%–35% of THC is urinary excreted. The compounds are highly protein-bound with a large volume of distribution, and therefore unlikely dialyzable [14]. In a survey aimed to evaluate nephrologist's view regarding cannabis use in dialysis patients, based on clinical experience, most nephrologists supported cannabinoids use for refractory symptoms of pain, decreased appetite, nausea, sleep disorders, etc., and encouraged clinical trials to assess safety and efficacy [22]. Such study will also have to further assess its pharmacokinetics properties among patients with ESKD.

Although participation in the trial was offered to all eligible patients, females were more reluctant to participate,

Table 2: Adverse events according to trial period and according to study drug treatment.

	Screening period (N = 18)	Treatment with WPE (N = 9)	Treatment with API (N = 6)	Treatment with placebo (N = 10)	Washout period (N = 11)	Follow-up period (N = 10)	Total
SAE							
Number of patients with SAE	3	3	1	2	0	1	NA
Number of SAE SAE considered possibly or definitely related to study drug	4	6	4	3	0	1	18
Death	0	2	0	0	0	0	2
Death	1	1	0	0	0	0	2
AE							
Number of patients with AE	2	8	6	8	5	3	NA
Number of AE	3	24	22	19	10	7	85
Number of AE leading to study drug discontinuation		2	1	1			
Severity assessment of AE and SAE							
Number of severe AE/SAE	3	5	2	0	0	1	11
Number of moderate AE/SAE	1	8	4	5	1	6	25
Number of mild AE/SAE	3	17	20	17	9	1	67

NA: not applicable.

therefore only two were screened. Consequently, gender differences in drug safety could not be tested. In the current study, there was a relatively high number of AEs regardless of treatment allocation. This could be explained by the population studies representing high risk patients with multiple comorbidities, and by their frequent interaction with healthcare professionals during HD sessions. Nevertheless, cannabis was not associated with a higher drug-related side effects compared with placebo, except for increased risk for somnolence, which generally improved with surveillance and careful dose management. The only SAE that was related to the study drug was an accidental overdose, which presented as tachycardia, hypertension and hallucinations which lasted a few hours, and was managed by closed supervision. API was also associated with two hypotensive episodes in one patient, which led to drug withdrawal; however, there was no evidence that blood pressure was affected significantly in others. There is concern for potential cardiovascular side effects of THC and CBD in patients with ESKD, though previous studies showed that under physiological conditions the effect of CBD on the cardiovascular system is negligible and regarded as harmless [23]. THC, on the other hand, has sympathomimetic features, which may increase the risk of blood pressure changes and tachycardia, especially when interacting with other drugs [24]. We were reassured that cannabis use in our study did not appear to be associated with an increased short-term cardiovascular risk.

Illicit cannabis use can be associated with hepatomegaly and elevated liver enzymes [25]. Cannabis was also related to increased hepatic enzymes in animal models [26]. Therefore, surveillance of liver enzymes was an important objective of the

study. Hepatocellular and cholestatic liver enzymes remained stable throughout study period indicating drug safety.

Cannabis is effective for pain management in diverse patient groups and indications [15, 27]. It may also improve sleep quality [28], uremic pruritus and other kidney disease-related symptoms [29]. As the main aim of this study was to assess safety, the study was underpowered to assess efficacy. Nevertheless, in patients using WPE, numerically fewer patients had appetite questionnaire score <14. Since pain is often accompanied by depression and anorexia [30], and as nutritional status is an important determinant of morbidity in patients with ESKD [31], this trend necessitates further study to assess the influence of cannabis use on appetite and nutritional status in patients treated with dialysis.

Pain management in patients with chronic kidney disease, particularly ESKD, is challenging, often starting with conservative tools [6] followed by pharmacologic therapy. The three-step analgesic ladder recommended by the WHO has been validated in patients with ESKD [32]. Acetaminophen is the drug of choice for mild pain, while non-steroidal anti-inflammatory drugs are generally avoided in patients with ESKD. Neuropathic pain can be treated with pregabalin or gabapentin, followed by an up-titration regimen of opioids for severe and intractable pain [33]. Opioids are chronically used in up to 50% of patients treated with HD [34], despite their multiple side effects, such as nausea, constipation and somnolence. Patients treated with opioids have also a higher prevalence of falls and fractures [35]. In addition, both their short- and long-term use is associated with increased morbidity and mortality in patients treated with HD [36]. Reduced opioids renal clearance may increase the risk of

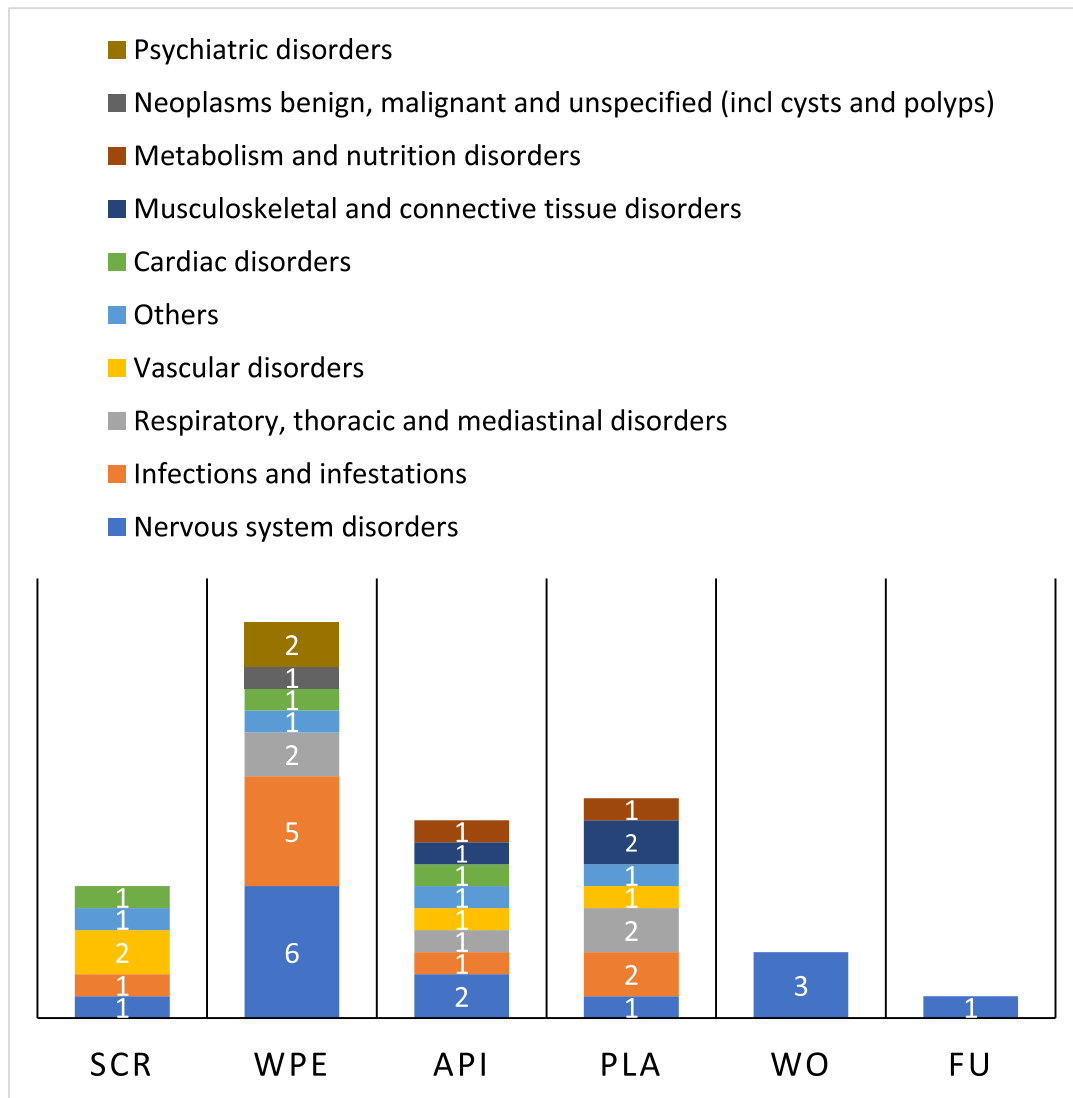


Figure 2: Adverse events by body system.

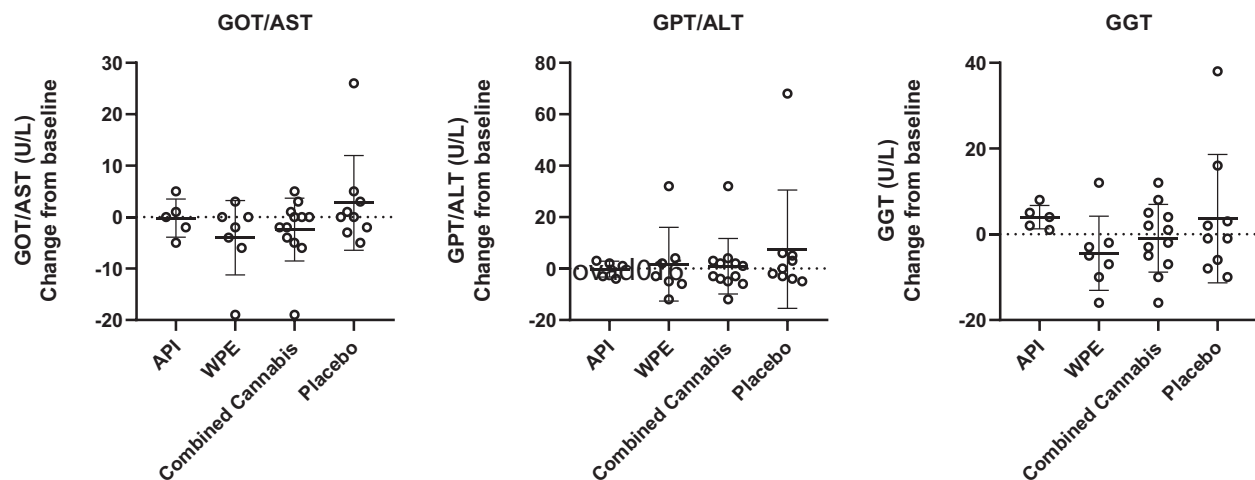


Figure 3: Change in liver enzymes: end of treatment vs treatment initiation.

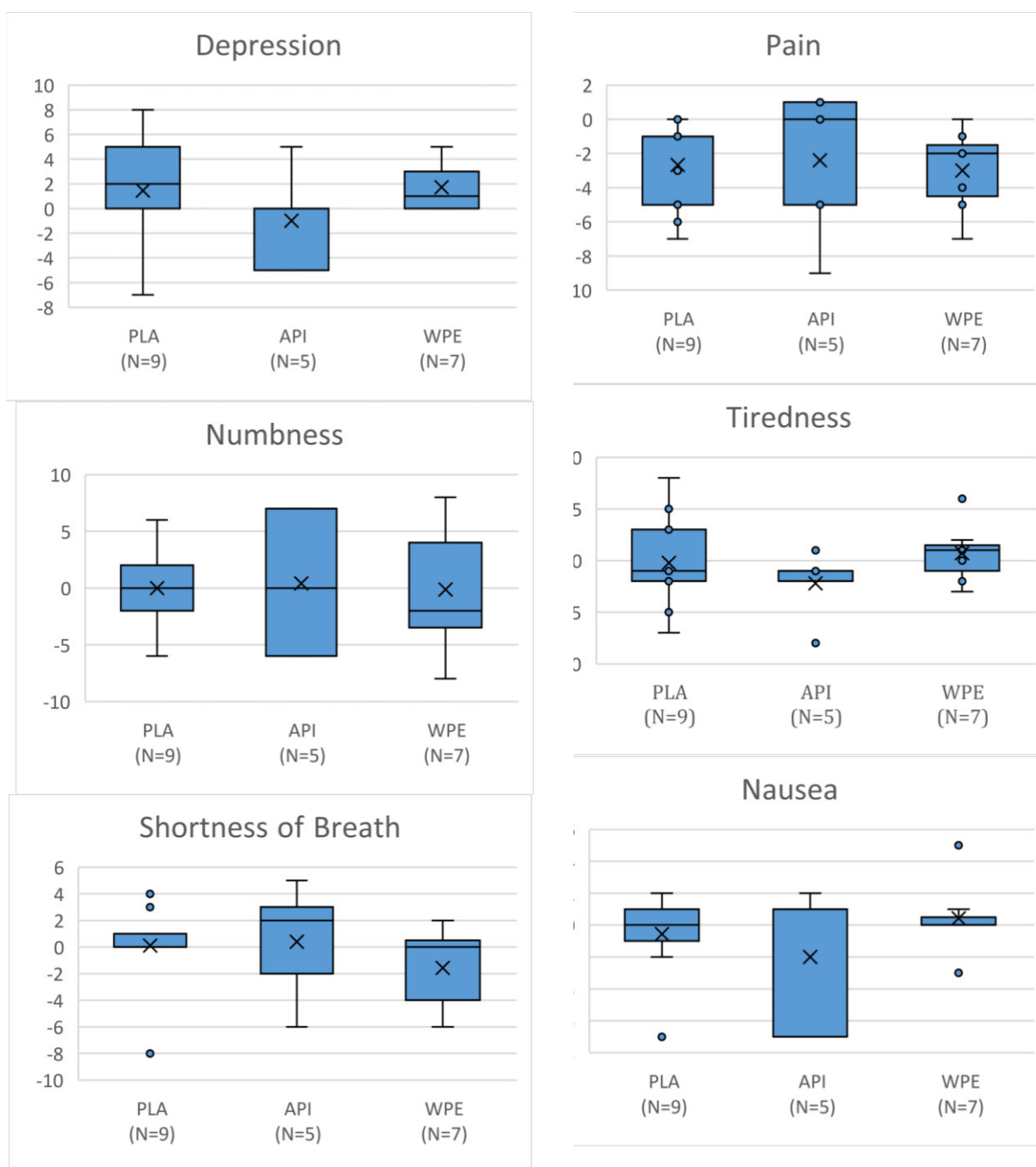


Figure 4: Difference in ESAS score relative to its baseline value.

drug overdose and side effects on one hand, while accelerated clearance during HD treatment may result in withdrawal symptoms on the other hand [35]. Our study provides prospective data regarding the safety of cannabis in patients treated with HD; further research is needed to assess its safety and efficacy compared with opioids or other strategies.

Limitations

The study was a feasibility study with safety as its main outcome and was underpowered to assess efficacy. Recruitment was slow

for several reasons: patients had other options for cannabis use and declined participation, others refused 3 months of cannabis avoidance before study entrance, some were concerned about using a drug perceived as illegal or feared side effects. It is possible that overly strict exclusion criteria also precluded study participation. These difficulties may have led to selection bias.

Questionnaires to assess symptoms were taken during screening and at the end of each treatment arm, but not before initiation of the second treatment period. Only VAS was documented at all visits. This can partially influence efficacy results. Drug titration was not identical in all patients, with protocol

deviations according to adverse events. This represents a recommendation for cannabis use in patients treated with HD, since drug dosage and titration should be tailored according to patients' characteristics and possible side effects, with close physician supervision.

CONCLUSIONS

A supervised, carefully titrated, short-term medical cannabis use in patients treated with HD was generally tolerated and was not associated with increased safety signals. Further studies are needed to assess safety and efficacy, in larger and more diverse populations with ESKD.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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AUTHORS' CONTRIBUTIONS

S.B., N.V., N.A. and O.K.-B.B. contributed to study design; O.M., M.S., I.Y., A.R. and O.K.-B.B. contributed to data acquisition and analysis, S.B., A.G., B.H. and O.M. helped in supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by BOL pharma by permission. Data will be shared on request to the corresponding author with permission of BOL pharma.

CONFLICT OF INTEREST STATEMENT

N.A. is an employee of BOL Pharma Ltd. N.V. and B.H. are former employees of BOL Pharma Ltd. O.M. is a former employee of BOL; Advisory Board: Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, AstraZeneca, Bayer, BOL Pharma; Research grant: Novo Nordisk, AstraZeneca; Speakers Bureau: Novo Nordisk, AstraZeneca, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim.

REFERENCES

1. Davison SN, Koncicki H, Brennan F. Pain in chronic kidney disease: a scoping review. *Semin Dial* 2014;**27**:188–204.
2. Davison SN. Pain in hemodialysis patients: prevalence, cause, severity, and management. *Am J Kidney Dis* 2003;**42**:1239–47.
3. Kliuk-Ben Bassat O, Brill S, Sharon H. Chronic pain is underestimated and undertreated in dialysis patients: a retrospective case study. *Hemodial Int* 2019;**23**:e104–5.
4. Fleishman TT, Dreier J, Shvartzman P. Pain in maintenance hemodialysis patients: a multicenter study. *J Pain Symptom Manage* 2018;**56**:178–84.
5. Santoro D, Satta E, Messina S et al. Pain in end-stage renal disease: a frequent and neglected clinical problem. *Clin Nephrol* 2013;**79**:S2–11.
6. Raina R, Krishnappa V, Gupta M. Management of pain in end-stage renal disease patients: short review. *Hemodial Int* 2018;**22**:290–6.
7. Wyne A, Rai R, Cuerden M et al. Opioid and benzodiazepine use in end-stage renal disease: a systematic review. *Clin J Am Soc Nephrol* 2011;**6**:326–33.
8. Kurella M, Bennett WM, Chertow GM. Analgesia in patients with ESRD: a review of available evidence. *Am J Kidney Dis* 2003;**42**:217–28.
9. Donvito G, Nass SR, Wilkerson JL et al. The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain. *Neuropsychopharmacology* 2018;**43**:52–79.
10. Romero-Sandoval EA, Fincham JE, Kolano AL et al. Cannabis for chronic pain: challenges and considerations. *Pharmacotherapy* 2018;**38**:651–62.
11. Namdar D, Anis O, Poulin P et al. Chronological review and rational and future prospects of cannabis-based drug development. *Molecules* 2020;**25**:4821.
12. Bonn-Miller MO, ElSohly MA, Loflin MJE et al. Cannabis and cannabinoid drug development: evaluating botanical versus single molecule approaches. *Int Rev Psychiatry* 2018;**30**:277–84.
13. Sharon H, Brill S. Cannabis-based medicines for chronic pain management: current and future prospects. *Curr Opin Anaesthesiol* 2019;**32**:623–8.
14. Ho C, Martinusen D, Lo C. A review of cannabis in chronic kidney disease symptom management. *Can J Kidney Health Dis* 2019;**6**:205435811982839.
15. Rein JL. The nephrologist's guide to cannabis and cannabinoids. *Curr Opin Nephrol Hypertens* 2020;**29**:248–57.
16. Caraceni A, Cherny N, Fainsinger R et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *J Pain Symptom Manage* 2002;**23**:239–55.
17. Spitzer RL, Kroenke K, Williams JB et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;**166**:1092–7.
18. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap* 1994;**23**:129–38.
19. Thong ISK, Jensen MP, Miró J et al. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure? *Scand J Pain* 2018;**18**:99–107.
20. Davison SN, Jhangri GS, Johnson JA. Longitudinal validation of a modified Edmonton symptom assessment system (ESAS) in haemodialysis patients. *Nephrol Dial Transplant* 2006;**21**:3189–95.
21. Wilson MM, Thomas DR, Rubenstein LZ et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr* 2005;**82**:1074–81.
22. Collister D, Tennankore K, Davison SN et al. Nephrologist views regarding cannabinoid use in advanced chronic

- kidney disease and dialysis: a survey. *J Pain Symptom Manage* 2021;**61**:237–45.e2.
23. Kicman A, Toczek M. The effects of cannabidiol, a non-intoxicating compound of cannabis, on the cardiovascular system in health and disease. *Int J Mol Sci* 2020;**21**:6740.
 24. Brown JD. Potential adverse drug events with tetrahydrocannabinol (THC) due to drug-drug interactions. *J Clin Med* 2020;**9**:919.
 25. Borini P, Guimarães RC, Borini SB. Possible hepatotoxicity of chronic marijuana usage. *Sao Paulo Med J* 2004;**122**:110–6.
 26. Kichloo A, Albosta M, Aljadah M et al. Marijuana: a systems-based primer of adverse effects associated with use and an overview of its therapeutic utility. *SAGE Open Med* 2021;**9**:205031212110009.
 27. Wallace MS, Marcotte TD, Umlauf A et al. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain* 2015;**16**:616–27.
 28. Haack M, Simpson N, Sethna N et al. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology* 2020;**45**:205–16.
 29. Samaha D, Kandiah T, Zimmerman D. Cannabis use for restless legs syndrome and uremic pruritus in in patients treated with maintenance dialysis: a survey. *Can J Kidney Health Dis* 2020;**7**:205435812095494.
 30. Gamondi C, Galli N, Schönholzer C et al. Frequency and severity of pain and symptom distress among patients with chronic kidney disease receiving dialysis. *Swiss Med Wkly* 2013;**143**:w13750.
 31. Hendriks FK, Kooman JP, van Loon LJC. Dietary protein interventions to improve nutritional status in end-stage renal disease patients undergoing hemodialysis. *Curr Opin Clin Nutr Metab Care* 2021;**24**:79–87.
 32. Barakzoy AS, Moss AH. Efficacy of the World Health Organization analgesic ladder to treat pain in end-stage renal disease. *J Am Soc Nephrol* 2006;**17**:3198–203.
 33. Koncicki HM, Unruh M, Schell JO. Pain management in CKD: a guide for nephrology providers. *Am J Kidney Dis* 2017;**69**:451–60.
 34. Bailie GR, Mason NA, Bragg-Gresham JL et al. Analgesic prescription patterns among hemodialysis patients in the DOPPS: potential for underprescription. *Kidney Int* 2004;**65**:2419–25.
 35. Tobin DG, Lockwood MB, Kimmel PL et al. Opioids for chronic pain management in patients with dialysis-dependent kidney failure. *Nat Rev Nephrol* 2022;**18**:113–28.
 36. Kimmel PL, Fwu CW, Abbott KC et al. Opioid prescription, morbidity, and mortality in United States dialysis patients. *J Am Soc Nephrol* 2017;**28**:3658–70.