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Original Article

Effects of sub-chronic nabiximols on biological markers of individuals undergoing a clinical trial for the treatment of cannabis use disorder

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Abstract: Objective: Nabiximols is used for treating various symptoms associated with multiple sclerosis (MS). Nabiximols is also being investigated as a potential treatment medication for individuals with cannabis use disorder (CUD). A variety of investigations have shown that, at low doses, nabiximols is overall well tolerated for MS treatment. However, due to tolerance, the management of CUD would likely require much higher doses of nabiximols to be effective. The effects of high doses of nabiximols on clinical laboratory tests remain unclear. Therefore, we investigated the sub-chronic effects of high doses of nabiximols on liver function, renal function, and other routine blood tests in this prospective study. Methods: We performed a secondary analysis of various blood markers results collected during a double-blind, placebo-controlled randomized clinical trial (Sativex and Behavioral-relapse Prevention Strategy in Cannabis Dependence, NCT01747850, https://clinicaltrials.gov/ct2/show/record/NCT01747850). This trial tested the impact of the 12-week administration of nabiximols with a maximum daily dose of up to 113.4 mg THC/105 mg CBD. Results: The measurements of the various biomarkers were in the normal range during the 12-week time frame. The results indicate an overall good tolerability of high-dose nabiximols on the blood markers measured. Conclusion: Our preliminary results suggest that high doses of nabiximols might be well tolerated by individuals with CUD.

Keywords: Nabiximols, blood marker, cannabis use disorder, treatment

Introduction

Nabiximols (Sativex®), originally approved to alleviate symptoms of multiple sclerosis (MS) in Canada and several European countries, has recently emerged as a potential agonist replacement therapy in treating cannabis use disorder (CUD). It is a cannabinoid buccal spray containing a mix of 27 mg/ml delta-9-tetrahydrocannabinol (THC) and 25 mg/ml cannabidiol (CBD) as active ingredients. The THC component of the medication provides the agonist replacement since it is a partial agonist of both cannabinoid type 1 (CB1) and type 2 (CB2) receptors [1]. On the other hand, CBD has been reported to antagonize the effect of agonists at CB1 and CB2 receptors [2], and to have antipsychotic [3] and anxiolytic [4] properties that could potentially counteract THC's psychomimetic and anxiogenic effects [5, 6]. Nabiximols contains both THC and CBD in a ~ 1:1 ratio and the two cannabinoids are believed to interact synergistically [7]. In fact, the adverse psychotropic effects associated with THC have been reported to be reduced by the coadministration of CBD in some studies [8, 9], but not all [10].

Table 1. Baseline demographic characteristics

Characteristic	Placebo (n=20)	Nabiximols (n=20)
	Mean (SD)	
Age (years)	35.3 (13.1)	30.7 (10.4)
	No. (%)	
Male	14 (70)	15 (75)
Female	6 (30)	5 (25)
Married/Common-Law	3 (15)	4 (20)
University/College	11 (55)	14 (70)
Full-time Employed	4 (20)	1 (5)

Therefore, we have previously tested nabiximols for its ability to reduce cannabis withdrawal symptoms [11] and reduce cannabis use [12].

When administered as a treatment to alleviate symptoms of MS, including spasticity and neuropathic pain, the dosage of nabiximols is generally restricted to a maximum of 12 sprays per 24-h period (i.e., up to 32.4 mg THC/30 mg CBD) [13, 14]. Multiple studies have also shown that, at low doses, nabiximols is well tolerated for MS treatment [13, 15-17]. However, due to the developed tolerance for cannabis in individuals with regular cannabis use, higher medication dosages might be required to achieve clinical efficacy when treating CUD [11].

Currently, controversial findings have been reported about the effects of nabiximols on clinical laboratory tests. In a previous study that administered nabiximols in treating MS patients, no significant changes in blood test results were found with a mean daily dose of 8 sprays [18]. When treating patients with peripheral neuropathic pain, there were again no apparent trends of biochemistry and hematology, with a mean dose of 8.9 sprays per day over a median treatment period of 78.2 days [19]. However, nabiximols was also reported to cause abnormal hematology and laboratory results. A study administering an average of 7.5 sprays per day, in the first year of nabiximols treatment, showed significant increases (i.e., over 20% of the upper limit of the normal range) in white blood cells (WBCs), mean corpuscular volume (MCV), and liver function tests occurred in a small subset of MS patients [20]. Increased WBCs and liver function tests, including elevated levels of aspartate transaminase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT), were also noticed in MS patients in another open-label trial of nabiximols administering an average daily dose of 10 sprays over 52 weeks [21]. In addition, increased alkaline phosphatase (ALP) and bilirubin were reported with one single case each in the same study [21]. Another study showed that in healthy participants, who were naive to cannabis or had not used cannabis or cannabinoid medication for three months before entering the study, eight nabiximols sprays for five days resulted in abnormal ALT levels in one participant, elevated AST and ALT levels in two participants who received 24 sprays, and resulted in high ALT levels for an additional participant who received 36 sprays, suggesting potential dose-related changes in clinical laboratory parameters [22]. However, to date, no other studies have implicitly analyzed the sub-chronic effects of high doses of nabiximols on clinical laboratory tests in individuals with CUD.

The main aim of our study was to assess the sub-chronic effects of high doses of nabiximols on liver function, renal function, and other routine blood tests for participants with CUD by performing a 12-week safety analysis, with a maximum daily dose of up to 113.4 mg THC/105 mg CBD, through an analysis of the blood test results collected during a double-blind, placebo-controlled randomized clinical trial.

Methods

This is a prospective study based on a secondary data analysis on plasma samples and clinical information collected by Trigo *et al.* [12]. Details of the original study procedures have been described previously [12]. Briefly, experimental sequences of the original study included a 12-week treatment period, during which the participants self-titrated the study medication of either placebo or nabiximols with a maximum of 42 sprays (a total of 113.4 mg THC/105 mg CBD) daily in combination with a weekly intervention of combined Motivational Enhancement Therapy and Cognitive Behavioral Therapy (MET/CBT), as well as a 3-month follow-up. Written informed consent was obtained from all participants.

Participants

The inclusion criteria for participants were: male or female; age between 18 to 56; meet

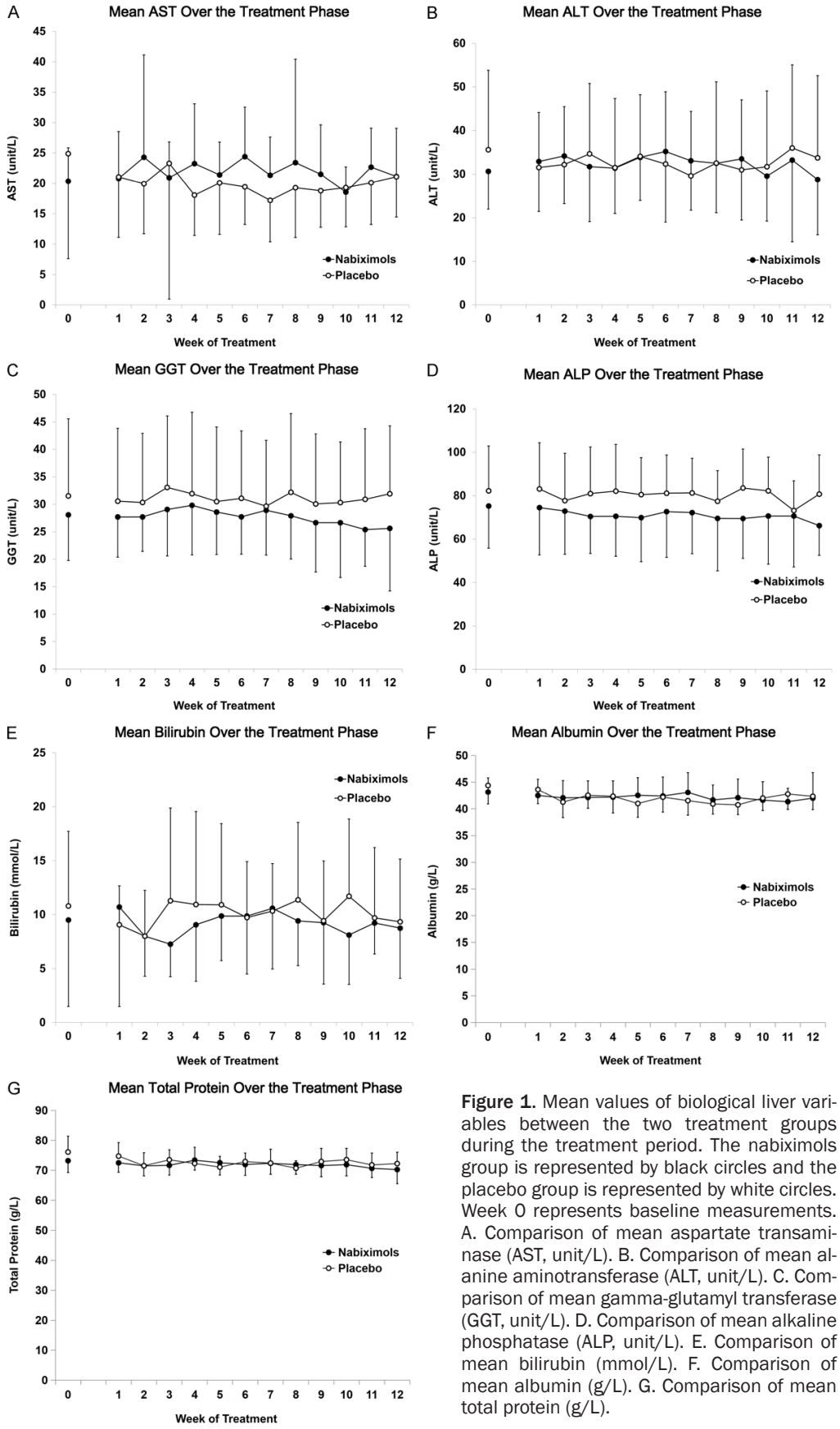

Figure 1. Mean values of biological liver variables between the two treatment groups during the treatment period. The nabiximols group is represented by black circles and the placebo group is represented by white circles. Week 0 represents baseline measurements. A. Comparison of mean aspartate transaminase (AST, unit/L). B. Comparison of mean alanine aminotransferase (ALT, unit/L). C. Comparison of mean gamma-glutamyl transferase (GGT, unit/L). D. Comparison of mean alkaline phosphatase (ALP, unit/L). E. Comparison of mean bilirubin (mmol/L). F. Comparison of mean albumin (g/L). G. Comparison of mean total protein (g/L).

Table 2. Effects of treatment, time, and treatment × time interaction for liver function tests, estimated by linear mixed models

	Treatment		Time		Treatment × Time	
	F	p	F	p	F	p
ALT	0.202	0.655	0.606	0.811	0.715	0.716
AST	1.590	0.213	0.855	0.588	1.308	0.251
GGT	0.264	0.610	1.604	0.135	0.698	0.732
ALP	2.917	0.096	2.406	0.025*	0.937	0.518
Bilirubin	0.333	0.568	1.922	0.068	1.465	0.186
Albumin	0.401	0.531	3.816	0.001*	2.742	0.013*
Total Protein	0.394	0.534	4.245	<0.001*	2.634	0.016*

Note: ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase. * denotes P<0.05.

the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for current cannabis dependence; willing to comply with study procedures; physical health conditions; stated cannabis as the primary drug of abuse; used cannabis at least five days per week for at least one month; seeking treatment for cannabis dependence; have a cannabinoid positive urine drug screen; smoke less than or equal to four grams of cannabis per day [12].

The exclusion criteria for participants were: history of seizures, cardiovascular disease, or pulmonary disease; meet DSM-IV criteria for a current Axis I disorder other can cannabis, nicotine, or caffeine dependence; have a first-degree relative with schizophrenia; unstable medical conditions; pregnant or breast-feeding; known sensitivity to ingredients of nabiximols buccal spray including dronabinol, cannabidiol, propylene glycol, ethanol, and peppermint oil; poor oral hygiene; currently taking psychotropic medications other than treatment of insomnia; having a job that requires driving or operating heavy machinery [12].

Nabiximols dosing

Nabiximols was self-titrated by the participants. There was a gradual increase in the maximum allowed dose of nabiximols, starting from five sprays per day for the first two days and followed by an increase of five sprays per day before reaching the number of 42 sprays maximum per day at day 10 (week 2). The medication treatment phase was continued for another nine weeks before reducing the maximum dose to 21 sprays per day for the final week (week 12).

Sample collection

Participants provided their blood samples at the baseline visit and during weekly visits throughout the treatment. Blood samples were collected at the conclusion of the study visits except on the first day of medication administration, during which the blood was drawn 30 minutes after the last nabiximols spray. Blood tests, including liver function tests, renal function tests, and other routine blood tests, were performed by the CAMH laboratory.

The components of liver function tests include: (i) ALT, (ii) AST, (iii) GGT, (iv) ALP, (v) bilirubin, (vi) albumin, and (vii) total protein. The components of renal function tests include: (i) estimate glomerular filtration rate (eGFR), (ii) blood urea nitrogen (BUN), (iii) creatinine, (iv) uric acid, (v) phosphate, and (vi) calcium. Other routine blood tests include: (i) red blood cells (RBCs), (ii) WBCs, (iii) platelets, (iv) hemoglobin, (v) MCV, and (vi) hematocrit (HCT).

Statistical analysis

A linear mixed model was used to analyze collected data with a covariate of the average weekly amount of cannabis used. The analysis also included case intercept random effects. Differences with *p*-values less than 0.05 were considered to be statistically significant. Values outside of the normal range were considered clinically significant variations. The Bonferroni correction was used for multiple comparisons. Post hoc pairwise comparisons between treatment groups for each week were performed when the initial linear mixed model yielded a significant difference in treatment-time interaction. Missing data were handled using restricted maximum likelihood estimation to utilize all the available information in the database. Data analysis was performed using the statistical software IBM SPSS Statistics version 28.0.1.1.

Ethical review

The original trial authorized by Health Canada was approved by the Centre for Addiction and Mental Health (CAMH) Research Ethics Board

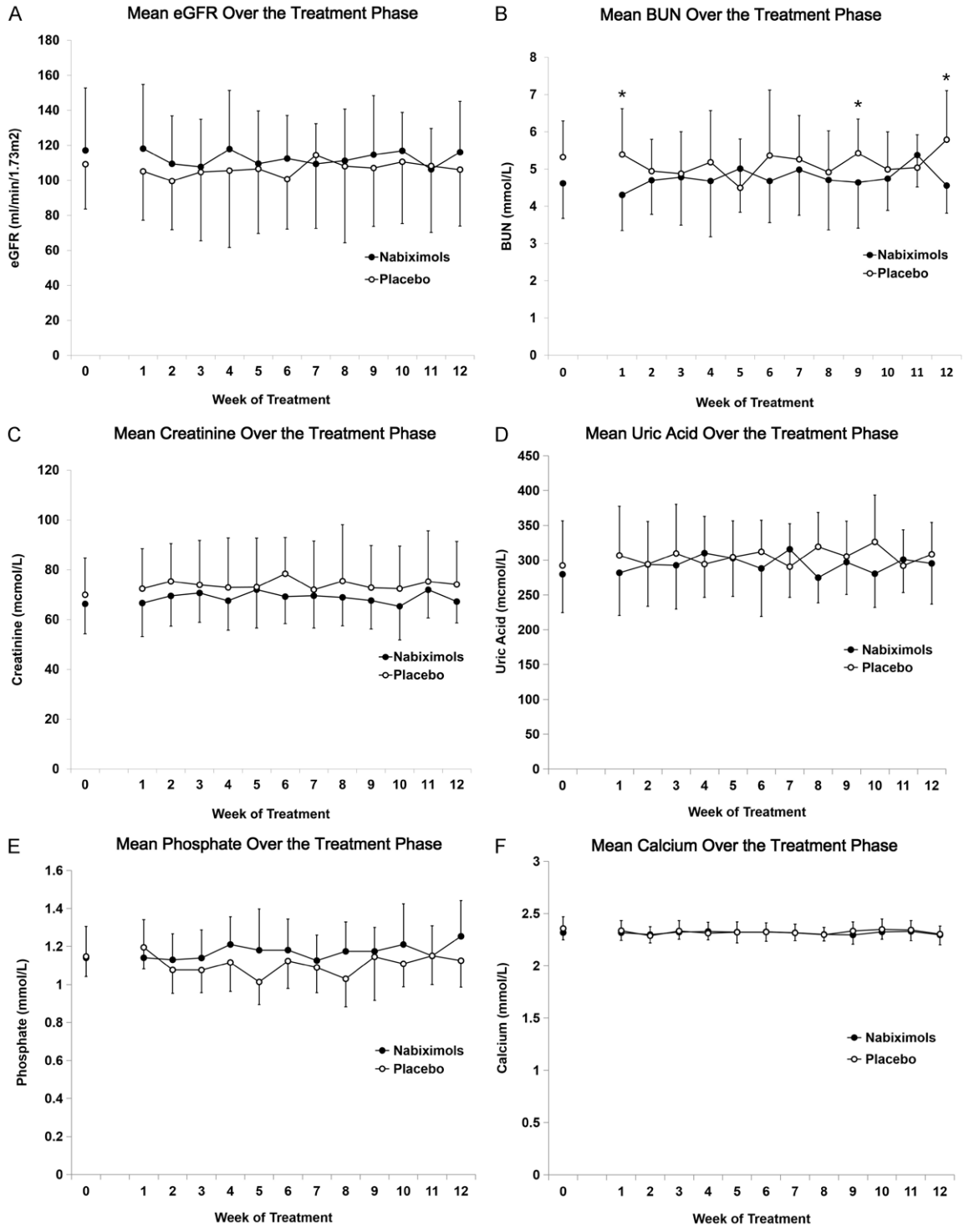

Figure 2. Mean values of biological renal variables between the two treatment groups during the treatment period. The nabiximols group is represented by black circles and the placebo group is represented by white circles. Week 0 represents baseline measurements. A. Comparison of mean estimate glomerular filtration rate (eGFR, ml/min/1.73 m^2). B. Comparison of mean blood urea nitrogen (BUN, mmol/L). C. Comparison of mean creatinine (mcmol/L). D. Comparison of mean uric acid (mcmol/L). E. Comparison of mean phosphate (mmol/L). F. Comparison of mean calcium (mmol/L). Note: * denotes $P<0.05$.

Table 3. Effects of treatment, time, and treatment × time interaction for renal function tests, estimated by linear mixed models

	Treatment		Time		Treatment × Time	
	F	p	F	p	F	p
eGFR	0.271	0.605	1.065	0.416	0.608	0.809
BUN	2.397	0.130	0.739	0.694	2.960	0.009*
Creatinine	0.396	0.533	0.958	0.499	0.767	0.670
Uric Acid	0.061	0.806	0.888	0.561	1.988	0.062
Phosphate	0.828	0.369	2.722	0.011*	1.173	0.338
Calcium	0.032	0.860	1.431	0.211	1.021	0.453

Note: eGFR, estimate glomerular filtration rate; BUN, blood urea nitrogen.
* denotes P<0.05.

(Protocol #144/2011) and was registered on ClinicalTrials.gov (NCT01747850).

Results

Participants

Sample characteristics have been described in detail elsewhere [12]. Briefly, a total of 368 participants were phone screened, and 89 of them completed the baseline assessment. Fifty participants were considered eligible to receive treatment, but ten withdrew from the study before being dosed. Then the remaining 40 participants were evenly separated into two groups of 20 before being randomly assigned to either the nabiximols treatment group or the placebo treatment group. Plasma samples were collected from those 40 participants. Seven participants withdrew from the nabiximols group, five withdrew from the placebo group, and one was excluded from the placebo group before the completion of the treatment phase. Therefore, a total of 27 participants completed the whole study. As shown in **Table 1**, the participants in the placebo treatment group were 35.3±13.1 years old on average, ranging from 21 to 64 years old; the participants in the nabiximols group were 30.7±10.4 years old on average, ranging from 20 to 60 years old.

Daily medication usage was self-reported by the participants using a smoking diary. On average, participants in the nabiximols group were administering doses ranging from 4.1 to 12.8 sprays per day (11.0 mg THC/10.2 mg CBD to 34.5 mg THC/31.9 mg CBD), while participants in the placebo group were administering doses ranging from 2.5 to 9.7 sprays per day (6.7 mg THC/6.2 mg CBD to 26.1 mg THC/24.2 mg CBD).

Liver function tests

The average test results of biological liver variables measured throughout the 12-week treatment period are presented in **Figure 1**. No significant trends from baseline to the end of the treatment could be observed for any of the variables, including ALT, AST, GGT, ALP, bilirubin, albumin, and total protein. As listed in **Table 2**, linear mixed models showed no significant differences between treatment conditions for any of the variables (P>0.05), but a significant effect of time for ALP (P=0.025), albumin (P=0.001), and total protein (P<0.001) with the addition of treatment × time interaction for albumin (P=0.013) and total protein (P=0.016). Post hoc pairwise comparisons showed no significant differences between treatment groups for albumin and total protein at any week (P>0.05).

Renal function tests

The average test results of biological renal variables measured throughout the 12-week treatment period are presented in **Figure 2**. No significant trends from baseline to the end of the treatment could be observed for any of the variables, including eGFR, BUN, creatinine, uric acid, phosphate, and calcium. As listed in **Table 3**, linear mixed models showed no significant differences between treatment conditions for any of the variables (P>0.05), but a significant effect of time for phosphate (P=0.011) and a significant treatment × time interaction for BUN (P=0.009). Post hoc pairwise comparisons showed significant differences between treatment groups for BUN at week 1 (P=0.004), week 9 (P=0.049), and week 12 (P=0.012).

Other routine blood tests

The average test results of other hematological parameters measured throughout the 12-week treatment period are presented in **Figure 3**. No significant trends from baseline to the end of the treatment could be observed for WBCs, platelets, hemoglobin, MCV, and HCT. Gradual decreases of RBCs could be observed for both

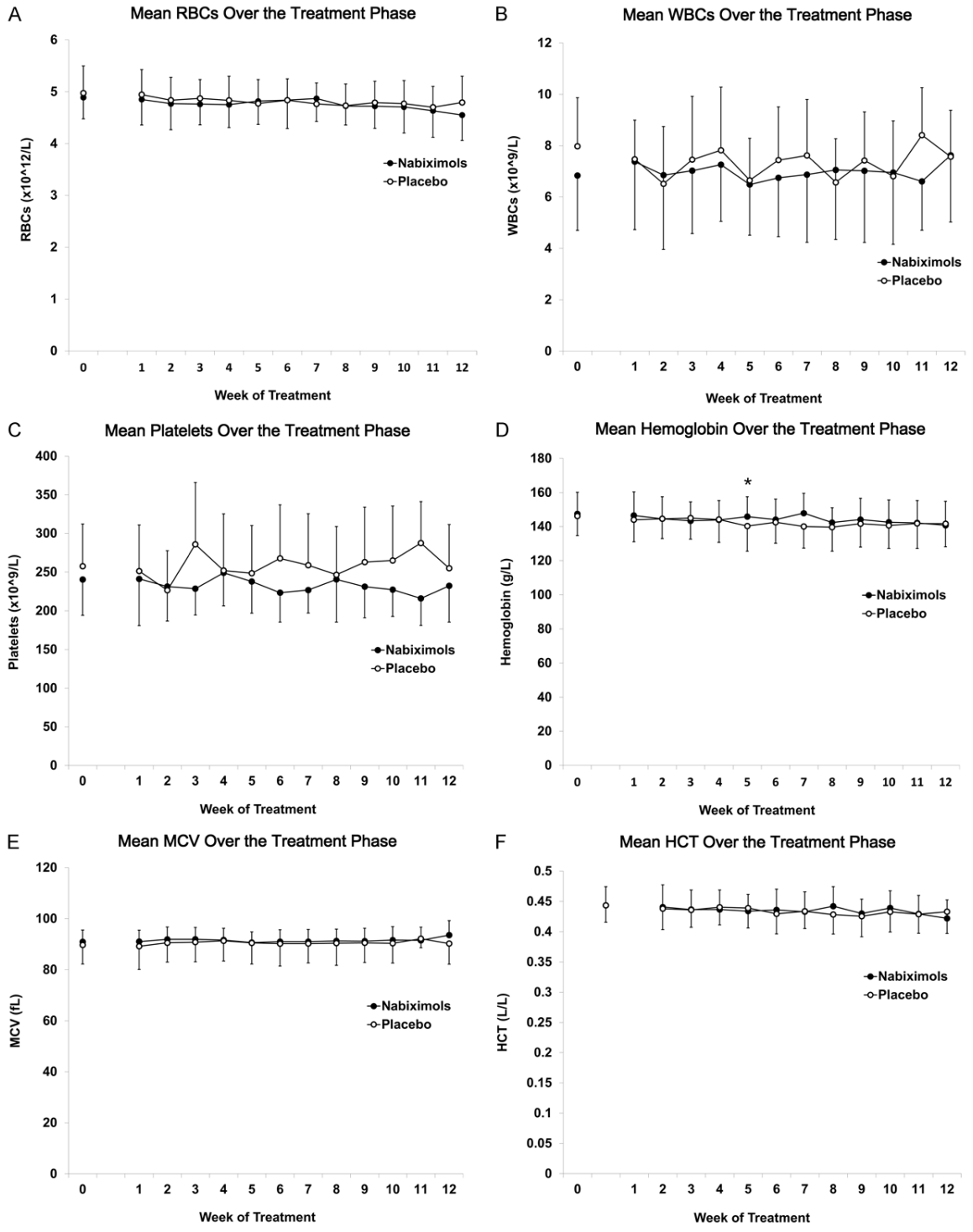

Figure 3. Mean values of other hematological parameters between the two treatment groups during the treatment period. The nabiximols group is represented by black circles and the placebo group is represented by white circles. Week 0 represents baseline measurements. A. Comparison of mean red blood cells (RBCs, ×10^12/L). B. Comparison of mean white blood cells (WBCs, ×10^9/L). C. Comparison of mean platelets (×10^9/L). D. Comparison of mean hemoglobin (g/L). E. Comparison of mean corpuscular volume (MCV, fL). F. Comparison of mean hematocrit (HCT, L/L). Note: * denotes $P<0.05$.

Table 4. Effects of treatment, time, and treatment × time interaction for other routine blood tests, estimated by linear mixed models

	Treatment		Time		Treatment × Time	
	F	p	F	p	F	p
RBCs	0.005	0.944	2.874	0.009*	1.863	0.082
WBCs	1.193	0.281	2.417	0.026*	1.136	0.369
Platelets	2.788	0.103	1.139	0.364	1.786	0.096
Hgb	1.043	0.314	4.467	<0.001*	2.388	0.025*
MCV	0.543	0.466	0.913	0.538	1.832	0.086
HCT	0.601	0.443	3.377	0.003*	1.385	0.227

Note: RBCs, red blood cells; WBCs, white blood cells; Hgb, hemoglobin; MCV, mean corpuscular volume; HCT, hematocrit. * denotes P<0.05.

the nabiximols group and the placebo group. As listed in **Table 4**, linear mixed models showed no significant differences between treatment conditions for any of the variables (P>0.05), but a significant effect of time for RBCs (P=0.009), WBCs (P=0.026), hemoglobin (P<0.001) and hematocrit (P=0.003) with the addition of treatment × time interaction for hemoglobin (P=0.025). Post hoc pairwise comparisons showed significant differences between treatment groups for hemoglobin at week 5 (P= 0.047).

Baseline and weekly biological measures

As listed in **Table 5**, the baseline and weekly measurements of liver function, renal function, and other routine blood tests in the nabiximols group participants all fell within the normal range.

Discussion

This study performed a 12-week safety analysis of nabiximols with a maximum daily dose of up to 113.4 mg THC/105 mg CBD by assessing its effects on liver function, renal function, and other routine blood tests for participants with CUD. As shown by linear mixed models, no significant differences in treatment-time interactions between placebo and nabiximols groups were observed over the 12-week treatment phase for all the conducted blood tests except for albumin, total protein, BUN, and hemoglobin. Post hoc pairwise comparisons revealed significant differences between the treatment groups in week 5 for hemoglobin and weeks 1, 9, and 12 for BUN but not in any of the weeks for albumin and total protein. Nevertheless, regardless of statistical significance, all measured blood test values fell within the expected normal range of a healthy person. Therefore, we can't conclude that there was a significant impact of nabiximols on the blood markers examined in this pilot study, suggesting that nabiximols, even at high doses tested in this study, could be well tolerated by individuals with cannabis dependence.

The participants in this study were all regular cannabis users, so they were likely to have already developed a tolerance to cannabinoids, as compared with drug-naive individuals, and therefore less likely to suffer any additional health issues after receiving oromucosal THC and CBD. Previous studies that administered nabiximols with doses up to 113.4 mg THC/105 mg CBD and treatment phases ranging from 8 weeks to 12 weeks in the treatment of CUD have demonstrated that nabiximols was well-tolerated even at high doses [11, 23, 24]. Our study thus further confirms the tolerability of nabiximols in our study population and extends insight into its safety profile in clinical laboratory tests.

The major limitation of this study was that the actual doses received by some participants were relatively low, which could be potentially attributed to the high variabilities in our dataset. As reported by participants using smoking diaries, only 9 participants in the nabiximols treatment group and 8 participants in the placebo treatment group self-administered greater than 20 sprays on any treatment day from week 1 to week 12. In comparison, 9 participants in the nabiximols treatment group and 11 participants in the placebo treatment group self-administered less than or equal to 20 sprays on all treatment days from week 1 to week 12. Another limitation was the small sample size of 20 participants in each treatment group. With low statistical power, the chances of detecting true effects were reduced. An additional limitation of this study is the missing values in the dataset due to participants missing study visits or other factors. Although maximum likelihood estimation was applied, the statistical power was still reduced, and biased results could potentially be produced. Our study population mainly consisted of male participants (i.e., 70% in the placebo groups and 75% in the

Table 5. Baseline and weekly measurements of liver function, renal function, and other routine blood tests of the nabiximols treatment group participants [mean (SD)]

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Reference Range
ALT (unit/L)	30.65 (8.68)	32.90 (11.47)	34.18 (10.93)	31.73 (12.62)	31.38 (10.40)	33.87 (9.87)	35.20 (16.21)	33.08 (11.36)	32.50 (11.35)	33.50 (14.06)	29.56 (10.32)	33.22 (18.75)	28.75 (12.63)	12-78
AST (unit/L)	20.35 (5.50)	20.8 (7.72)	24.29 (16.83)	20.93 (5.89)	23.25 (9.83)	21.40 (5.40)	24.40 (8.13)	21.33 (6.29)	23.42 (17.03)	21.50 (8.13)	18.56 (4.16)	22.67 (6.40)	21.13 (7.94)	15-37
GGT (unit/L)	28.10 (8.35)	27.70 (7.34)	27.71 (6.30)	29.07 (8.49)	29.81 (9.03)	28.60 (7.75)	27.73 (6.81)	28.92 (8.17)	27.92 (7.88)	26.67 (9.00)	26.67 (10.01)	25.40 (6.70)	25.63 (11.41)	5-55
ALP (unit/L)	75.25 (19.49)	74.50 (21.83)	72.94 (19.95)	70.47 (17.11)	70.56 (18.53)	69.93 (20.36)	72.67 (21.08)	72.25 (19.01)	69.58 (24.22)	69.50 (18.43)	70.67 (22.23)	70.67 (23.54)	66.25 (13.73)	46-116
Bilirubin (mmol/L)	9.50 (8.01)	10.70 (9.22)	8.00 (3.71)	7.27 (3.01)	9.06 (5.23)	9.87 (4.12)	9.87 (5.37)	10.58 (5.62)	9.42 (4.14)	9.25 (5.69)	8.11 (4.57)	9.22 (2.86)	8.75 (4.65)	0.0-17.9
Albumin (g/L)	43.15 (2.66)	42.5 (3.03)	42.06 (3.25)	42.13 (3.09)	42.19 (3.04)	42.53 (3.36)	42.4 (3.58)	43.08 (3.73)	41.67 (2.81)	42.08 (3.53)	41.63 (3.46)	41.33 (2.55)	42 (4.78)	34-50
Total Protein (g/L)	73.2 (3.98)	72.5 (3.12)	71.5 (3.39)	71.67 (3.24)	73.38 (3.32)	72.53 (4.12)	71.93 (3.59)	72.33 (3.63)	71.92 (3.20)	71.58 (3.70)	71.89 (3.72)	70.67 (3.04)	70.25 (4.65)	64-82
eGFR (ml/min/1.73 m^2)	117.16 (35.63)	118.15 (36.62)	109.47 (27.32)	107.73 (27.19)	117.88 (33.53)	109.53 (30.12)	112.47 (24.57)	109.42 (22.98)	111.25 (29.47)	114.67 (33.74)	116.89 (21.89)	106.33 (23.40)	116.13 (29.07)	60-120
BUN (mmol/L)	4.62 (0.94)	4.31 (0.96)	4.70 (0.91)	4.79 (1.29)	4.68 (1.50)	5.01 (1.17)	4.68 (1.12)	4.98 (1.22)	4.71 (1.34)	4.64 (1.23)	4.74 (0.85)	5.38 (0.86)	4.56 (0.74)	2.5-6.4
Creatinine (mcmol/L)	66.34 (12.09)	66.67 (13.51)	69.54 (12.12)	70.69 (11.80)	67.60 (11.82)	72.03 (15.40)	69.26 (10.85)	69.60 (12.95)	68.93 (11.42)	67.67 (11.43)	65.36 (13.56)	71.98 (11.33)	67.26 (8.58)	62.0-115.0
Uric Acid (mcmol/L)	279.8 (55.01)	281.85 (61.61)	293.71 (59.85)	292.6 (63.08)	310.13 (63.68)	302.8 (54.85)	288.07 (69.00)	315.67 (69.21)	274.92 (36.35)	297.08 (46.42)	280.56 (48.69)	300.89 (47.34)	295.25 (58.39)	208-428
Phosphate (mmol/L)	1.14 (0.16)	1.14 (0.20)	1.13 (0.14)	1.14 (0.15)	1.21 (0.15)	1.18 (0.22)	1.18 (0.16)	1.13 (0.13)	1.17 (0.15)	1.17 (0.13)	1.21 (0.21)	1.15 (0.16)	1.25 (0.19)	0.81-1.58
Calcium (mmol/L)	2.32 (0.07)	2.32 (0.08)	2.30 (0.08)	2.32 (0.07)	2.33 (0.08)	2.32 (0.10)	2.33 (0.09)	2.32 (0.08)	2.30 (0.07)	2.30 (0.09)	2.32 (0.07)	2.33 (0.09)	2.30 (0.10)	2.12-2.52
RBCs (×10^12/L)	4.89 (0.41)	4.85 (0.49)	4.77 (0.50)	4.76 (0.40)	4.75 (0.44)	4.82 (0.45)	4.84 (0.55)	4.87 (0.44)	4.72 (0.37)	4.72 (0.43)	4.71 (0.50)	4.63 (0.51)	4.55 (0.49)	4.50-6.00
WBCs (×10^9/L)	6.83 (2.13)	7.37 (2.64)	6.85 (2.90)	7.02 (2.45)	7.26 (2.20)	6.48 (1.97)	6.74 (2.28)	6.87 (2.63)	7.05 (2.70)	7.02 (2.79)	6.95 (2.79)	6.60 (1.90)	7.63 (2.61)	3.50-10.00
Platelets (×10^9/L)	240.32 (46.16)	241.20 (60.35)	231.29 (44.60)	228.53 (33.93)	249 (42.63)	237.73 (40.79)	223.40 (37.89)	226.83 (29.76)	240.50 (55.01)	231.17 (40.13)	227.22 (34.58)	216 (35.01)	232.25 (46.81)	130-400
Hgb (g/L)	147.42 (12.72)	146.45 (13.95)	144.53 (13.02)	143.33 (11.25)	143.88 (11.47)	145.80 (11.78)	144.07 (12.11)	147.83 (11.73)	142.33 (8.77)	144.08 (12.59)	142.56 (13.09)	142.10 (13.24)	140.67 (14.23)	135-170
MCV (fL)	90.94 (4.63)	91.03 (4.49)	91.89 (4.85)	91.93 (4.63)	91.64 (4.60)	90.67 (4.16)	91.01 (4.67)	91.01 (4.76)	91.28 (4.62)	91.19 (5.06)	91.61 (5.30)	91.52 (5.16)	93.58 (5.67)	82.0-96.0
HCT (L/L)	0.444 (0.031)	0.441 (0.037)	0.437 (0.032)	0.437 (0.032)	0.434 (0.028)	0.436 (0.034)	0.433 (0.033)	0.442 (0.032)	0.430 (0.024)	0.439 (0.028)	0.429 (0.030)	0.422 (0.030)	0.424 (0.032)	0.390-0.470

Note: ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; eGFR, estimate glomerular filtration rate; BUN, blood urea nitrogen; RBCs, red blood cells; WBCs, white blood cells; Hgb, hemoglobin; MCV, mean corpuscular volume; HCT, hematocrit.

nabiximols group), which could result in a limitation in the generalizability of the study data. Future studies might assess the prolonged (i.e., >12 weeks) effects on the safety and tolerability of nabiximols in large groups of individuals with cannabis dependence.

Conclusion

The results obtained in this pilot study indicated that there was no significant impact of subchronic high-dose nabiximols treatments on blood markers of liver function, renal function, and other hematological parameters, suggesting that nabiximols could be well tolerated by individuals with CUD.

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