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Efficacy and safety of Cannabidiol and Tetrhydrocannabinvarin on glycaemic and lipid parameters in patients with Type 2 diabetes: a randomised, double-blind, placebo-controlled, parallel group pilot study

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Short title: CBD and THCV in humans with type 2 diabetes
Abstract

Objective Cannabidiol (CBD) and delta-9-tetrahydrocannabivarin (THCV) are non-psychoactive phytocannabinoids affecting lipid and glucose metabolism in animal models. This study set out to examine the effects of these compounds in patients with type 2 diabetes.

Research Design and Methods In this randomised, double-blind, placebo-controlled study, 62 subjects with non-insulin treated type 2 diabetes were randomised to five treatment arms; CBD (100 mg twice daily), THCV (5 mg twice daily), 1:1 ratio of CBD and THCV (5 mg:5 mg, twice daily), 20:1 ratio of CBD and THCV (100 mg:5 mg, twice daily), or matched placebo, for 13 weeks. The primary endpoint was a change in HDL-cholesterol concentrations from baseline. Secondary/tertiary endpoints included changes in glycaemic control, lipid profile, insulin sensitivity, body weight, liver triglyceride content, adipose tissue distribution, appetite, markers of inflammation, markers of vascular function, gut hormones, circulating endocannabinoids and adipokine concentrations. Safety and tolerability endpoints were also evaluated.

Results Compared with placebo, THCV significantly decreased fasting plasma glucose (estimated treatment difference (ETD)=-1.2mmol/L, \( P<0.05 \)) and improved pancreatic β-cell function (homeostasis model assessment (HOMA2 B) (ETD=-44.51 points, \( P<0.01 \)), adiponectin (ETD=-5.9 x 10^6pg/mL, \( P<0.01 \)) and apolipoprotein A (apoA) (ETD=-6.02µmol/L, \( P<0.05 \)), although plasma HDL was unaffected. Compared to baseline (but not placebo), CBD decreased resistin (-898 pg/ml, \( P<0.05 \)) and increased glucose-dependent insulinotropic peptide (21.9 pg/ml, \( P<0.05 \)). None of the combination treatments had a significant impact on endpoints. CBD and THCV were well tolerated.
Conclusions   THCV could represent a new therapeutic agent in glycaemic control in subjects with type 2 diabetes.
The endocannabinoid system (ECS) modulates food intake and energy homeostasis (1, 2) and chronic over-activation of the ECS has been identified in obesity and type 2 diabetes (3). The ECS exerts some of its actions by various components activating cannabinoid receptors 1 (CB₁) and 2 (CB₂). Modulation of CB₁ receptors with rimonabant (a synthetic cannabinoid) led to a significant reduction in body weight, waist circumference and triglyceride (TG) concentrations, and an increase in HDL-cholesterol and adiponectin concentrations (4), as well as a reduction in HbA1c in subjects with type 2 diabetes (-0.8% to –1.25%, P<0.001). However, marketing authorisation for rimonabant was withdrawn in 2008 because of an increased incidence of psychiatric adverse events (AEs) (5). Rimonabant is thought to be a CB₁ receptor antagonist/inverse agonist, but it is unclear whether modulation of other cannabinoid receptor activity could have beneficial metabolic effects without significant psychiatric effects.

Cannabidiol (CBD) is one of the major phytocannabinoids obtained from the Cannabis sativa L. plant. In rodent studies, CBD has multiple desirable effects in the context of hyperglycaemia, mainly through its anti-inflammatory and anti-oxidant properties (6-10). In animal models of obesity (ob/ob genetically obese mice), four weeks treatment with CBD 3mg/kg, produced a 55% increase in HDL-C concentration and reduced total cholesterol (total-C) by more than 25% (GW Pharma data on file). In addition, the same dose reduced liver triglycerides and increased both liver glycogen and adiponectin concentration. There is also evidence from animal studies showing that CBD modulates cardiovascular response to stress (11).

Unlike the related molecule ∆⁹-tetrahydrocannabinol (THC), CBD does not activate CB₁ receptors in the brain and therefore lacks the psychotropic actions of THC. Indeed, CBD may reduce psychosis (12) and mitigate the psychoses associated with
cannabis misuse (13). Other receptor sites implicated in the actions of CBD include the orphan G-protein coupled receptor-55 (GPR55), the putative endothelial cannabinoid receptor (CBr), the transient receptor potential vanilloid 1 (TRPV1) receptor, α1-adrenoceptors, µ opioid receptors, the adenosine transporter and serotonin-1A (5-HT1A) receptors (14). CBD also activates and has physiological responses mediated by peroxisome proliferator activated receptor γ (PPARγ) (15, 16, 17). A CBD/THC combination (Sativex®/Nabiximols) is currently licensed in most EU countries and in Canada, New Zealand, Australia, Malaysia, the United Arab Emirates and Kuwait, for the symptomatic treatment of spasticity in moderate to severe multiple sclerosis, and CBD alone (Epidiolex®) was granted orphan drug designation by the FDA in February 2014 in Dravet and Lennox-Gastaut syndromes in children, with Phase 3 clinical trials ongoing in those conditions.

Δ9-tetrahydrocannabivarin (THCV) is a naturally occurring analogue of THC, but with different pharmacological effects. It is has been reported to behave as both a CB1/CB2 agonist and/or a CB1/CB2 neutral antagonist (20, 21, 22, 23, 24), probably dose-dependent, with agonism observed at high doses and antagonism at low doses (21). However, there is little evidence of CB1 agonism in vivo compared with the observed in vivo effects of THC at similar doses. Other target sites of action include GPR55 (25) and transient receptor potential channels (26, 27).

Acute intraperitoneal administration of THCV in rodents at 3, 10 and 30 mg/kg body weight, caused hypophagia and weight loss, with food intake and body weight returning to normal on day 2 (18). The effect was similar to that of a CB1 antagonist AM251, also used in the same study. In another study, involving diet-induced obese (DIO) mice, oral THCV (2.5 to 12.5 mg/kg) reduced body fat content, increased energy expenditure, and reduced fasting insulin and 30 min insulin response to oral
glucose tolerance test (OGTT) (19). In the same study, in genetically obese \((ob/ob)\) mice, a similar increase in 24-hour energy expenditure was observed with 3mg/kg THCV, while 12.5 mg/kg THCV caused a significant reduction in liver triglycerides (19). In genetically obese mice \((ob/ob)\), a 1:1 ratio of a combination of THCV and CBD (3 mg/kg:3 mg/kg) reduced total cholesterol levels by 19% and increased HDL-C by 50%. The same combination reduced liver TG, increased liver glycogen levels, reduced fasting insulin and increased energy expenditure (GW Pharma data on file).

The findings from these preclinical studies demonstrate a potential beneficial effect of both CBD and THCV, alone or in combination, in diabetes and lipid metabolism, with very distinct pharmacological profiles, and therefore different side effects, to rimonabant. This prompted the first ever investigation of the effects of CBD and THCV on dyslipidaemia and glycaemic control in subjects with type 2 diabetes.

**Research Design and Methods**

*Subjects and study design*

This randomised, double-blind, placebo-controlled, parallel-group, phase 2a proof-of-concept study was conducted at four United Kingdom centres. The protocol was reviewed and approved by the East Midlands - Leicester Multi Centre Research Ethics Committee (10/H0406/42) and local R&D departments as required, and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.
Subjects aged 18 years or above with type 2 diabetes and HbA1c ≤10% (86 mmol/mol), HDL-C ≤1.3mmol/L in females and ≤1.2mmol/L in males, and plasma triglycerides ≤10mmol/L, were eligible. Subjects needed to either receive no oral hypoglycaemic agents or take stable doses of pre-specified non-insulin glucose lowering therapies (metformin, sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor or glucagon-like peptide-1 (GLP-1) therapy) for three months prior to screening. Subjects not on statin therapy or on a stable dose of a statin, for at least four weeks prior to randomisation, were eligible for inclusion. Subjects were also required not to make any changes to their diet or exercise for four weeks prior to randomisation and during the course of the study.

Main exclusion criteria (see supplemental data for full details) included use of prohibited medications (insulin, fibrates, thiazolidinediones, therapeutic omega-3 fatty acids, alpha-glucosidase inhibitors), recent or current use of cannabis, history of significant depression, planned travel outside the UK during the course of study, genetic dyslipidaemia or significant cardiac, renal or hepatic impairment.

There was a one to five week period between screening (visit 1) and treatment randomisation (visit 2). Visit 1 could be split into two separate visits (1A and B) to allow a 21-day washout period of the prohibited medications prior to blood sampling for eligibility. Remaining visits occurred 4, 8 and 13 weeks after initiation of treatment (visits 3, 4 and 5, respectively), or earlier if patients withdrew. A safety follow up visit occurred 7 days after study completion or withdrawal (visit 6). Visits 4 and 6 were telephone assessments.
Patients were required to take study medication in the fasted state, twice daily, 30 minutes before breakfast and 30 minutes before evening meal, typically 12 hours apart for 13 weeks.

**Study endpoints and assessments**

The primary endpoint was change in mean serum HDL-C from baseline, in CBD and THCV groups, compared with the change in placebo group, at week 13. Secondary endpoints included changes in lipid profile, glycaemic control, insulin sensitivity, body weight, visceral adiposity, appetite and cardiovascular function. Tertiary endpoints were changes in markers of inflammation, vascular function, adipokines, endocannabinoids and gut hormone concentrations.

Serum lipid concentrations were analysed with the Roche modular system using enzymatic calorimetric assays. Non-esterified fatty acid (NEFA) concentrations were quantified on the Roche COBAS 311 system, using an acyl-CoA synthetase/acyl-CoA oxidase (ACS-ACOD) method. Apolipoprotein markers were analysed on the Roche COBAS 311 system, using immunoturbidimetric assays, based on the principle of immunological agglutination. Plasma VLDL-C concentrations were determined by ultracentrifugation.

A standard 75 g OGTT was performed and plasma glucose and serum insulin were analysed using the Roche modular system and Advia Centaur immunoassay analyser respectively. HOMA-insulin resistance (IR), insulin sensitivity and β-cell function were calculated using the HOMA2 Calculator v2.2© (Diabetes Trials Unit, University of Oxford).

Plasma endocannabinoids, N-arachidonoylethanolamine (AEA), 2-arachidonoylglycerol (2-AG), oleylethanolamine (OEA) and palmitoylethanolamine
(PEA), were analysed using liquid chromatography-tandem mass spectrometry, based on a previously published method (28). Ketones, orexin A and retinol binding protein (RBP) 4 were analysed using immunoassay, while all other tertiary endpoints including adiponectin, resistin, leptin, E-Selectin, vascular cell adhesion molecule (VCAM), Von Willebrand factor (vWF), C-reactive protein (CRP), interleukin (IL) 6, tumour necrosis factor (TNF) α, glucose-dependent insulinotropic peptide (GIP), ghrelin and GLP-1 were analysed by multiplex analysis, using commercially available kits (Milliplex™, HMHMAG-34K, HCVD1-67AK, HADK-1-61K-A, HCVD2-67BK, BPHCVD05-6, Merck Millipore®).

Resting blood pressure was measured using digital blood pressure monitor while cardiovascular parameters including systolic, diastolic and mean arterial pressure, heart rate, stroke volume, cardiac output, inter beat interval, ejection time and total peripheral resistance were measured using a Finometer® (Finapres Medical Systems), which uses a finger-clamp method to detect beat-to-beat changes in digital arterial diameter with an infrared photoplethysmograph.

Adipose tissue distribution was assessed using whole body magnetic resonance imaging (MRI); images were analysed by a blinded investigator using SliceOmatic™. Body weight and 7-point skin fold measures were also recorded. Hepatic TG concentration was assessed using magnetic resonance spectroscopy (MRS) and analysed using JMRUI software

Subject’s Global Impression of Change (SGIC) and Clinician’s Global Impression of Change (CGIC) was assessed using an ordinal 7-point Likert scale (1=very much improved to 7=very much worse). Changes in appetite were established using patients’ scores of their appetites that they recorded on daily basis using an appetite
0-10 numerical rating scale (NRS), where 0=no appetite (don’t feel hungry) and 10=maximum appetite (completely hungry all the time) (29). The change from mean baseline score (mean of seven days before start of treatment) was compared to the mean score from the last seven days on treatment (end of 13 weeks).

Safety assessments included reporting for adverse events (AEs) and serious adverse events (SAEs), recording vital signs, pre- and post-treatment laboratory sampling and electrocardiograms (ECG) and change from baseline in Beck Depression Inventory-II (BDI-II) scores.

The BDI-II questionnaire, an assessment for anxiety and depression, is a multiple choice, self-reported inventory, and is one of the most widely used and validated instruments for measuring severity of depression (30).

**Statistical methods**

An independent statistician produced a schedule for random treatment allocation which was held centrally and not divulged to any other person involved in the study until the database had been locked. Patients were randomly allocated to treatment groups in a 1:1:1 ratio, stratified by centre, according to the randomisation schedule. Study site staff identified the pack number to be dispensed to the subject at each of Visits 2 and 3 according to the randomisation schedule.

Analysis was performed using the intention-to-treat (ITT) population; all subjects who were randomised, received at least one dose of study medication and had on-treatment efficacy data. All statistical tests were two-sided at the 5% significance level. Between group differences and 95% confidence intervals (CI) were also calculated. The primary endpoint and the majority of secondary endpoints were analysed using analysis of covariance (ANCOVA) of the changes from baseline to
the end of treatment in the associated parameter, with the exception of the SGIC and CGIC, which were analysed with ordinal logistic regression using the cumulative proportional odds model. The parameter’s baseline values were included as a covariate, and treatment was included as a factor. The tertiary variables were analysed using ANCOVA with baseline value as covariate and treatment group and gender as factors, or using pairwise Fisher’s Exact test, as appropriate. The null hypothesis was one of no difference in the effects of any of the active treatments compared individually with placebo. As this study was a phase 2a proof of concept study, no formal sample size calculation was performed.

Changes from baseline in all the plasma markers were analysed post hoc using a paired t-test, and the glucose response to OGTT was analysed using repeated measures 2-way ANOVA.

Results

One hundred and twenty-five patients were screened and 62 randomised to the five treatment arms. The disposition of subjects enrolled is presented in Figure 1. Subjects were similar between treatment groups (Table 1) in terms of baseline characteristics.

Lipids

THCV had no effect on HDL-C concentrations (Table 2), but it increased Apo A concentrations compared with placebo from baseline to the end of treatment (from 48.5 to 49.1 µmol/L in the THCV vs. 47.3 to 43.9 µmol/L in the placebo group;
P<0.05, Fig. 2A). THCV had no effect on LDL-C concentrations. CBD alone and in combination with THCV, did not affect any of the lipid parameters (Table 2).

**Glycaemic Control**

THCV reduced fasting plasma glucose concentration compared with placebo from baseline to the end of treatment (from 7.4 to 6.7 mmol/L in the THCV vs. 7.6 to 8.0 mmol/L in the placebo group, ETD = -1.24 ± 0.6 (SEM), P<0.05, Fig. 3A). In line with this, there was a significant increase in HOMA2 B in the THCV treatment group compared with placebo from baseline to the end of treatment (from 105.1 to 144.4 in the THCV group vs. 96.4 to 94.7 in the placebo group, ETD = 44.6 ± 16.1 (SEM), P<0.01, Table 2, Fig 3B). There was no significant difference in glucose response to OGTT at 2 hours. However, when compared with baseline, THCV significantly improved 3-hour blood glucose response (P<0.05, Fig 3C). CBD alone or in combination with THCV had no effect on glycaemic parameters (Table 2).

**Vascular Function**

Compared to placebo, CBD and THCV, alone and in combination, had no effect on cardiovascular parameters (Table 2), or plasma markers of vascular function (Supplementary data Table 1).

**Adipokines**

There was an increase from baseline in adiponectin concentration in the THCV group and a reduction in placebo group; the treatment difference was statistically significant in favour of THCV treatment (ETD -5.9 x 10^6 pg/mL, P<0.01, Fig. 3B). Plasma concentrations of leptin and resistin remained unchanged with THCV treatment. Compared with baseline rather than placebo, CBD caused a significant
reduction in the concentration of resistin (-898 pg/mL, \(P<0.05\), Fig. 3C), but had no effect on leptin or adiponectin. Subjects taking a combination of CBD and THCV had no change in adipokine levels (Supplementary data Table 1).

**Markers of Inflammation**

Both THCV and CBD, or their combination, had no significant effect on plasma markers of inflammation (CRP, TNF \(\alpha\) and IL-6; supplementary data Table 1).

**Gut Hormones**

THCV, on its own and in combination with CBD, had no effect on the concentrations of gut signalling hormones including GLP-1, GIP and ghrelin (supplementary data Table 1). However, in a post-hoc analysis, for which post-treatment concentrations were compared with baseline (rather than placebo), CBD caused a significant increase in the concentration of GIP (21.2 pg/mL, \(P<0.05\), Fig. 3D), without any effect on GLP-1 or ghrelin concentrations.

**Body weight**

Baseline mean body weight (kg ± SD) in the CBD, THCV, 1:1 CBD:THCV, 20:1 CBD:THCV and placebo groups were 97.1 ± 13.8, 98.3 ± 17.5, 100.7 ± 14.5, 100.5 ± 17.9 and 94.2 ± 19.1 respectively. There were no statistically significant changes in anthropometric parameters including weight, waist circumference, waist to hip ratio and skin fold thickness in any of the treatment groups (Table 2).

**Visceral adiposity and liver triglycerides**

There were no changes in visceral adiposity or liver TG (Table 2) as assessed by MRI/MRS in any of the treatment groups.
Appetite

None of the treatments had any significant impact on appetite as assessed by 0-10 NRS scores (Table 2).

PGIC and CGIC

A full summary of the PGIC and CGIC assessment responses is presented in Supplemental Figures 1 and 2. Analysis of these responses showed a treatment difference in favour of all the active treatments, to varying degrees, but most notably between the 1:1 CBD:THCV and placebo treatment groups on CGIC. There were reported improvements in seven out of 11 (63.6%) patients in the CGIC on 1:1 CBD:THCV treatment, compared with only two of the 14 (14.3%) placebo patients, with a recorded improvement on CGIG. This translated to a statistically significant treatment effect of 1:1 CBD:THCV treatment compared with placebo, with an odds ratio of 9.529 ($P<0.05$) in the CGIC. No other statistically significant effects were calculated for any other active treatment in either assessment.

Endocannabinoids

There was no significant change in the levels of circulating AEA, 2-AG, OEA and PEA after 13 weeks of any treatment (Table 2).

Post hoc analysis in THCV group analysing glucose response to OGTT and changes in HbA1c

An improvement in glucose response to OGTT was noted in the THCV group at 3 h (see Fig 3C). When subjects on any form of diabetes treatment other than diet/metformin were excluded from analysis, this effect became more pronounced.
In the same group of diet/metformin only patients, compared with placebo, a significant improvement in HbA1c was also observed ($P<0.05$, Fig 3D).

**Safety**

The study medication was well tolerated, with the majority of subjects experiencing AEs that were mild or moderate in severity. Treatment-emergent (all causality) AEs were reported by 11 of 13 (84.6%) subjects in the CBD group, 11 of 12 (91.7%) in the THCV group, 7 of 11 (63.6%) in the 1:1 CBD:THCV group, 8 of 11 (66.7%) in the 20:1 CBD:THCV group, compared with 13 of 14 subjects (92.9%) receiving placebo.

The more common treatment-related AE reported by subjects in all the groups, except for 20:1 CBD:THCV, was decreased appetite (two subjects (15.4%) receiving CBD, four subjects (33.3%) receiving THCV, one subject (9.1%) receiving 1:1 CBD:THCV and two subjects (14.3%) receiving placebo). None of the subjects in 20:1 CBD:THCV group experienced an AE of decreased appetite. Two subjects reported diarrhoea with THCV, compared to no subjects in the placebo group. Two subjects (14.3%) on placebo also reported dizziness. All other treatment-related AEs were reported in individual subjects.

No deaths occurred during the study. There were two SAEs in this study. One patient (8.3%) taking 20:1 CBD:THCV treatment experienced an SAE of myocardial infarction that was considered moderate in severity, had recovered by the end of study, and was not considered to be treatment related. One placebo patient experienced an SAE of myocardial ischaemia that was not considered to be treatment-related, was mild in severity and occurred on Day 92 of the study; the SAE was still ongoing at the end of the study.
Mean changes from screening to the end of treatment in BDI-II scores for the CBD, THCV and 1:1 CBD:THCV treatment groups were 0.85, 0.58 and 0.27 points, respectively, which were not statistically significant from placebo (change from baseline of 0.08 points), and remained within the ‘minimal depression’ range for all treatments. The largest change from baseline to the end of treatment in BDI-II score was in the 20:1 CBD:THCV treatment group (4.91 points). While this remained in the ‘minimal depression’ bracket, it was statistically significant compared to placebo (ETD = 4.77, P<0.01).

**Conclusions**

The aim of this pilot study was to investigate the clinical effect and tolerability of two phytocannabinoids, THCV and CBD, alone and in combination, in subjects with type 2 diabetes and dyslipidaemia. THCV significantly decreased fasting plasma glucose, and increased β-cell function, adiponectin and Apo A concentrations, and was well tolerated in patients. These findings suggest that THCV may represent a new therapeutic agent for glycaemic control in subjects with type 2 diabetes.

The ECS plays an important role in modulating energy intake and expenditure (for reviews, see 1, 2), and a chronically over active ECS may have a role in diabetes and its various complications (2). A recent cross-sectional study showed that marijuana use was associated with lower concentrations of fasting insulin, insulin resistance and waist circumference (31). Some of the favourable metabolic effects seen with smoking cannabis may be due to partial CB₁ agonists like THC, which may act as a functional antagonist in conditions of increased endocannabinoid tone like obesity, because of its lower CB₁ binding affinity and efficacy in comparison to 2-AG, whose levels are elevated in visceral obesity (32). Rimonabant, a CB₁ receptor
antagonist, was the first in its class to be used as anti-obesity drug, but led to significant psychiatric adverse events (5). Pre-clinical studies with the plant-derived compound THCV have shown that it produces hypophagia and weight reduction in lean mice (18) and improves glucose tolerance and insulin sensitivity in DIO mice (19). Similar results have been seen with CBD in *ob/ob* mice (GW Pharma data on file) and CBD has been reported to lower the incidence of diabetes in non-obese diabetic mice (33), and arrest the onset of autoimmune diabetes in non-obese diabetic mice (34). Given the positive metabolic effects of both THCV and CBD in preclinical studies and their potent anti-inflammatory and antioxidant properties (22,35,36), we decided to investigate, for the first time, their efficacy and tolerability in subjects with type 2 diabetes.

**THCV Alone**

THCV treatment alone had no effect on HDL-C concentration. It did, however, produce a significant rise in serum Apo A, when compared with placebo. Apo A makes 90% of HDL protein and constitutes an important structural component of the HDL particle. Apo A I, which accounts for 70% of the Apo A (the remaining 20% accounted for by Apo A II), plays an important role in reverse cholesterol transport (37). The significance of this result remains unclear.

THCV significantly reduced fasting blood glucose concentrations, improved HOMA2 B and improved the 3-hour blood glucose response to OGTT, without any significant difference in insulin response. These findings are in keeping with the recent animal data, where THCV improved fasting glucose and 30 min glucose response to OGTT, and also improved insulin sensitivity by reducing fasting and post glucose insulin concentrations (19). In the same study, THCV treatment improved insulin-induced
phosphorylation of Akt (also known as protein kinase B) in insulin-resistant human hepatocytes and mice myotubes, suggesting improved insulin signalling as one of the possible mechanisms of action.

Although there was an improvement in fasting and 3-hour post OGTT blood glucose, there were no changes in body weight and gut hormone concentrations. In fact, a rise in the concentration of retinol binding protein 4 (RBP-4) was observed with THCV, an adipokine that has been associated with obesity and insulin resistance (38). Therefore the mechanism by which THCV improves glycaemic control remains unclear.

THCV significantly increased adiponectin concentrations. Adiponectin enhances hepatic insulin sensitivity, increases fatty acid oxidation and has important anti-atherogenic properties. Its concentrations are reduced in obesity and type 2 diabetes (39).

Positive metabolic effects of THCV on glycaemic control and adiponectin concentrations were also seen with rimonabant, the first CB₁ antagonist to be licenced as anti-obesity medication that was later withdrawn from market due to increased incidence of psychiatric adverse events (5). It is, however, important to emphasize that while rimonabant consistently reduced body weight in all the reported randomised clinical trials, no such change was seen with THCV, suggesting clear differences in the mechanisms of action of these compounds. Recent animal data with THCV similarly showed no effect on body weight (19). Moreover, rimonabant improved the lipid profile (increased HDL-C and reduced TG levels), while THCV had no effect on lipid parameters in our study (40). There is also a clear difference in chemical structure between THCV and rimonabant. It is therefore reasonable to believe that THCV and rimonabant have different pharmacological and
safety profiles. At micromolar concentrations, THCV inhibits the activity of both fatty acid amide hydrolase (FAAH) and monoacyl glycerol lipase (MAGL), thereby inhibiting the hydrolysis of AEA and 2-AG respectively (41). THCV, therefore, can act as an indirect agonist at the cannabinoid receptors, by enhancing the activity of the endocannabinoid system. Since such a change was not seen in our study, it is reasonable to believe that, at the dose tested, THCV was unable to modulate the endocannabinoid system. Recent animal data from Wargent and colleagues (19) showed that most of the positive metabolic effects of THCV were seen with 5 and 12.5 mg/kg doses given orally in rodents. In comparison to this, the dose used on our study (10 mg/day, approx. 0.1 mg/kg in humans) was much lower.

**CBD Alone**

Although CBD did not produce any effects on the primary and secondary efficacy outcomes compared with placebo, it reduced circulating resistin concentrations from baseline, while increasing the concentration of circulating GIP. Increased concentrations of resistin are associated with obesity and insulin resistance (42). GIP is one of the incretin hormones, produced by K cells in the proximal duodenum, which is known to have insulinotropic and pancreatic β-cell preserving properties (43). Despite having positive effects on resistin and GIP, CBD did not produce any improvement in glycaemic control.

CBD is known for its indirect agonism at the CB$_1$ receptors, by either increasing CB$_1$ constitutional activity or the endocannabinoid tone. CBD has been reported to inhibit hydrolysis of AEA by FAAH (but only at high micromolar levels) and also increases 2-AG levels (39). In a recent clinical study, in subjects with schizophrenia, 800 mg per day of CBD treatment significantly increased serum AEA levels and was
associated with an improvement in clinical profile of these subjects (12). In our study, CBD (albeit at a much lower dose), alone or in combination with THCV, had no effect on the plasma levels of endocannabinoids, suggesting that it had minimal interaction with the endocannabinoid system at the doses investigated.

Studies in rodents have used intraperitoneal CBD in a dose ranging from 1 mg/kg/day to 20 mg/kg/day, with positive effects on the metabolism seen only with higher dose ranges (7, 8, 9). In a 70 kg individual, a 20 mg/kg/day dose equates to 1400 mg/day. Similarly, human studies have used CBD in higher doses (12, 44). The dose used in our study was 200 mg/day, which could possibly explain lack of therapeutic effects seen with CBD.

**Combination of CBD and THCV**

Except for an improvement in CGIC assessments with 1:1 CBD:THCV treatment, none of the efficacy parameters were affected by 1:1 or 20:1 combination of CBD and THCV. There was a trend towards an improvement in most lipid parameters and the overall incidence of all-causality treatment related AEs was lowest in the 1:1 CBD:THCV treatment group; these factors could have led to an impression of improvement in subjects' overall condition with this treatment. While the combination of CBD and THCV did not produce any favourable effects on any of the parameters, the favourable effects of THCV were also lost in the combination treatment. Similarly, the positive effects of CBD on GIP and resistin were not seen in any of the combination treatments. This suggests that CBD and THCV in combination may counteract their individual therapeutic effects at least in the ratios and doses tested in this study. This may be at the level of receptors or due to interference with each other’s metabolism or therapeutic half-life, and requires further investigation.
Safety

Both CBD and THCV were well tolerated, with the majority of patients experiencing AEs that were mild in severity. The most common AE was reduced appetite with similar incidence across all the treatment groups. There were no reports of depression and no clinically significant abnormalities on ECG and laboratory results including blood count, liver and renal biochemistry in any treatment groups. There was one SAE of myocardial ischaemia in the placebo group, and one SAE of myocardial infarction in the 20:1 CBD:THCV group; both were considered unrelated to study medication. With regards to the BDI-II scale, though the change in 20:1 CBD:THCV treatment group was statistically significant, all mean active treatments and placebo scores remained in the ‘minimal depression’ range.

Conclusion

In this clinical study, the first to study the effects of CBD and THCV in subjects with type 2 diabetes and dyslipidaemia, THCV improved glycaemic control, and therefore warrants further investigation in this therapeutic area. CBD failed to show any detectable metabolic effects despite producing desirable changes in some adipokines and gut hormone concentrations. The incidence of AEs was similar between treatment groups, and both CBD and THCV were well tolerated. No new safety concerns were identified in the study.

Conflicts of interest and source of funding

SHR has been a member of GW’s Speaker’s Board and has received funding for clinical studies. GT is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme. The views expressed are those of GT and not necessarily those of the NHS, the NIHR or the Department of Health.
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Dr Stephen Wright of GW Pharmaceuticals is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions:

K.J. involved in study design, researched data, wrote manuscript, reviewed/edited manuscript. S.R. recruited patients, reviewed/edited manuscript. D.B. researched data, reviewed/edited manuscript. E.T. researched data. C.S. involved in study design, reviewed/edited manuscript. J.B. researched data, reviewed/edited manuscript. S.O’S involved in study design, wrote manuscript, reviewed/edited manuscript. G.T. involved in study design, chief investigator, wrote manuscript, reviewed/edited manuscript.

We would like to thank Lesley Taylor and Heather Lauder of GW Pharmaceuticals for their help with preparing the manuscript.
Figure legends

**Figure 1.** Summary of breakdown of patients enrolled in the study. 125 subjects were screened and 62 randomised to this study.

**Figure 2.** Compared with placebo, THCV alone caused a significant improvement in the concentration of Apo A ($P<0.05$; A) and adiponectin ($P<0.01$; B). Data was analysed by analysis of covariance and presented as mean ± SEM. CBD caused a significant reduction in resistin ($P<0.05$; C) and an increase in GIP concentration ($P<0.05$; D), when compared with pre-treatment values. Data were analysed *post hoc* using paired t-test and presented as mean ± SEM.

**Figure 3.** Compared with placebo, THCV alone caused significant improvement in fasting glucose ($P<0.05$; A) and in keeping with this, there was a highly significant improvement in β cell function measured by HOMA2 ($P<0.01$; B). THCV caused significant improvement in 3 hour glucose response during OGTT ($P<0.05$; C), when compared with pre-treatment values.

Data were analysed using 2-way ANOVA and presented as mean ± SEM. (D) Compared with pre-treatment values, there was a highly significant improvement in 3 hour glucose response to OGTT with THCV, when subjects on any oral hypoglycaemic therapy other than diet and/or metformin were excluded from analysis ($P<0.01$, n=6). In the same subgroup (analysed post hoc), compared with placebo, there was a statistically significant improvement in HbA1c ($P<0.05$, E). Data were analysed *post hoc* using repeated measures 2 way ANOVA and paired t-test respectively and presented as mean ± SEM.
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Figure 1

Screened (n=125)
Randomised (n=62)

CBD (n=13)
- Withdrew (n=1)
- Met withdrawal criteria (n=1)
- Completed (n=12)
- Analysis (n=13)

THCV (n=12)
- Withdrew (n=2)
- Adverse event (n=2)
- Completed (n=10)
- Analysis (n=10)

1:1 CBD:THCV (n=11)
- Withdrew (n=0)
- Completed (n=11)
- Analysis (n=11)

20:1 CBD:THCV (n=12)
- Withdrew (n=2)
- Adverse event (n=2)
- Completed (n=10)
- Analysis (n=12)

Placebo (n=14)
- Withdrew (n=1)
- Withdrawn by investigator (n=1)
- Completed (n=13)
- Analysis (n=14)
Figure 2
Figure 3
Table 1. Summary of patient demographics and concomitant therapy.

<table>
<thead>
<tr>
<th></th>
<th>CBD (n=13)</th>
<th>THC (n=12)</th>
<th>1:1 CBD:THC (n=11)</th>
<th>20:1 CBD:THC (n=12)</th>
<th>Placebo (n=14)</th>
<th>Total (n=62)</th>
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</thead>
<tbody>
<tr>
<td>Male (number of subjects and (%))</td>
<td>10 (77)</td>
<td>10 (83)</td>
<td>6 (55)</td>
<td>9 (75)</td>
<td>7 (50)</td>
<td>42 (68)</td>
</tr>
<tr>
<td>Female (number of subjects and (%))</td>
<td>3 (23)</td>
<td>2 (17)</td>
<td>5 (45)</td>
<td>3 (25)</td>
<td>7 (50)</td>
<td>20 (32)</td>
</tr>
<tr>
<td>Age (years, Mean (SD))</td>
<td>56.8 (9.9)</td>
<td>62.5 (12.6)</td>
<td>59.3 (8.8)</td>
<td>58.0 (8.1)</td>
<td>58.6 (7.7)</td>
<td>59.0 (9.4)</td>
</tr>
<tr>
<td>Weight (kg, Mean (SD))</td>
<td>97.2 (13.8)</td>
<td>98.3 (17.5)</td>
<td>100.7 (14.5)</td>
<td>100.5 (17.9)</td>
<td>94.2 (19.1)</td>
<td>98.0 (16.4)</td>
</tr>
<tr>
<td>BMI (kg/m² Mean (SD))</td>
<td>33.2 (5.4)</td>
<td>34.0 (6.5)</td>
<td>36.4 (5.6)</td>
<td>35.4 (4.6)</td>
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<td>34.4 (5.8)</td>
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<tr>
<td>Duration since diagnosis of diabetes (years, Mean (SD))</td>
<td>2.8 (3.3)</td>
<td>4.8 (3.6)</td>
<td>4.4 (2.7)</td>
<td>5.1 (3.3)</td>
<td>3.8 (3.5)</td>
<td>4.2 (3.3)</td>
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</table>

Number (%) of patients on anti-diabetic and lipid lowering therapy

<table>
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<tr>
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<th>CBD (n=13)</th>
<th>THC (n=12)</th>
<th>1:1 CBD:THC (n=11)</th>
<th>20:1 CBD:THC (n=12)</th>
<th>Placebo (n=14)</th>
<th>Total (n=62)</th>
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</thead>
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<tr>
<td>Metformin</td>
<td>9 (69)</td>
<td>9 (75)</td>
<td>10 (91)</td>
<td>11 (92)</td>
<td>12 (86)</td>
<td>51 (82)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>1 (9)</td>
<td>1 (8)</td>
<td>1 (7)</td>
<td>5 (8)</td>
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<tr>
<td>Sulfonylureas</td>
<td>3 (23)</td>
<td>5 (42)</td>
<td>4 (36)</td>
<td>3 (25)</td>
<td>4 (29)</td>
<td>19 (31)</td>
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<tr>
<td>Statins</td>
<td>9 (69)</td>
<td>11 (92)</td>
<td>10 (91)</td>
<td>8 (67)</td>
<td>13 (93)</td>
<td>51 (82)</td>
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</table>
Table 2. Clinical data before (baseline) and after (treatment) 13 weeks of randomised treatment

<table>
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<tr>
<th>Variable</th>
<th>CBD (n=13)</th>
<th>THCV (n=12)</th>
<th>1:1 CBD : THCV (n=11)</th>
<th>20:1 CBD : THCV (n=12)</th>
<th>Placebo (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.0 ± 0.3</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Total-C (mmol/l)</td>
<td>4.5 ± 0.9</td>
<td>3.8 ± 0.9</td>
<td>3.7 ± 1.0</td>
<td>4.2 ± 1.1</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>2.5 ± 0.7</td>
<td>2.0 ± 0.8</td>
<td>2.2 ± 0.8</td>
<td>2.0 ± 0.5</td>
<td>2.8 ± 0.6</td>
</tr>
<tr>
<td>HDL:LDL-C ratio</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.3</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>UC VLDL-C (mmol/l)</td>
<td>0.8 ± 0.4</td>
<td>1.0 ± 0.7</td>
<td>0.9 ± 0.7</td>
<td>1.0 ± 0.4</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.2 ± 1.4</td>
<td>1.7 ± 1.1</td>
<td>1.8 ± 1.5</td>
<td>2.4 ± 1.6</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>Apo A (μmol/l)</td>
<td>48.6 ± 9.7</td>
<td>48.5 ± 7.0</td>
<td>49.1 ± 6.4</td>
<td>48.7 ± 11.1</td>
<td>45.7 ± 6.3</td>
</tr>
<tr>
<td>Apo B (μmol/l)</td>
<td>3.1 ± 0.8</td>
<td>2.6 ± 0.6</td>
<td>2.7 ± 1.0</td>
<td>3.0 ± 0.9</td>
<td>3.4 ± 0.7</td>
</tr>
<tr>
<td>Apo B:Apo A ratio</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.2</td>
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<tr>
<td>NEFA (mmol/l)</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.6</td>
<td>0.7 ± 0.7</td>
<td>0.6 ± 0.2</td>
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<tr>
<td></td>
<td>Liver TG (%)</td>
<td>Fasting glucose (mmol/l)</td>
<td>Fructosamine (µmol/l)</td>
<td>HbA1c (%)</td>
<td>Glucose - 2 h OGTT (mmol/l)</td>
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<td></td>
<td>26.9 ± 16.9</td>
<td>8.0 ± 2.3</td>
<td>259.5 ± 34.4</td>
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<td>7.4 ± 2.7</td>
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<td>22.2 ± 17.1</td>
<td>8.4 ± 2.8</td>
<td>256.8 ± 44.6</td>
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<td>11.9 ± 8.0</td>
<td>7.4 ± 2.3</td>
<td>238.3 ± 25.0</td>
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<td>11.5 ± 13.5</td>
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<td>239.3 ± 28.7</td>
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<td>33.3 ± 18.3</td>
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<td>254.4 ± 35.7</td>
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<td>32.2 ± 26.2</td>
<td>8.4 ± 2.8</td>
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<td>25.4 ± 15.1</td>
<td>7.6 ± 1.4</td>
<td>268.8 ± 58.2</td>
<td>7.3 ± 1.3</td>
<td>6.6 ± 2.3</td>
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<td>18.5 ± 15.4</td>
<td>8.0 ± 1.6</td>
<td>241.4 ± 19.3</td>
<td>7.0 ± 0.7</td>
<td>7.9 ± 2.6</td>
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</table>

Note: Values are means ± standard deviation.
<p>| | | | | | | | | | |</p>
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<td></td>
<td>1.0 ± 0.05</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.05</td>
<td>1.0 ± 0.06</td>
<td>1.0 ± 0.05</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.05</td>
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<td><strong>Waist-to-hip ratio</strong></td>
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<td>42.1 ± 3.7</td>
<td>42.8 ± 3.8</td>
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<td>41.7 ± 4.8</td>
<td>41.1 ± 4.8</td>
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<td><strong>Neck circumference (cm)</strong></td>
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<td>8.5 ± 2.2</td>
<td>9.1 ± 3.5</td>
<td>9.0 ± 3.5</td>
<td>8.5 ± 3.0</td>
<td>8.6 ± 2.7</td>
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<td>5.6 ± 1.0</td>
<td>4.9 ± 1.0</td>
<td>5.4 ± 1.7</td>
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<td>4.7 ± 1.2</td>
<td>3.6 ± 1.6</td>
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<td>4.1 ± 1.9</td>
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<td>133.4 ± 16.4</td>
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<td>126.4 ± 11.6</td>
<td>134.3 ± 12.8</td>
<td>132.7 ± 11.0</td>
<td>134.2 ± 14.8</td>
<td>137.2 ± 11.9</td>
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<td><strong>Systolic BP (mmHg)</strong></td>
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<td>70.6 ± 8.8</td>
<td>70.6 ± 12.2</td>
<td>71.0 ± 9.4</td>
<td>73.2 ± 6.8</td>
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<td>70.5 ± 15.7</td>
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<td>77.1 ± 12.1</td>
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<td><strong>Diastolic BP (mmHg)</strong></td>
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<td>3.3 ± 3.3</td>
<td>4.5 ± 5.2</td>
<td>4.7 ± 5.0</td>
<td>2.8 ± 2.7</td>
<td>7.9 ± 7.6</td>
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<tr>
<td><strong>BDI-II score</strong></td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.05</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
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<tr>
<td><strong>AEA</strong></td>
<td>5.0 ± 2.9</td>
<td>4.7 ± 2.9</td>
<td>4.3 ± 1.7</td>
<td>13.6 ± 28.6</td>
<td>6.2 ± 3.1</td>
<td>5.0 ± 1.5</td>
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<td>3.7 ± 3.3</td>
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<td>2.4 ± 1.1</td>
<td>1.8 ± 0.7</td>
<td>2.4 ± 1.0</td>
<td>2.3 ± 0.6</td>
<td>2.5 ± 0.8</td>
<td>2.2 ± 0.7</td>
<td>2.2 ± 0.8</td>
<td>2.4 ± 0.5</td>
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<tr>
<td><strong>2-AG</strong></td>
<td>2.7 ± 1.9</td>
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<td>2.4 ± 1.2</td>
<td>2.6 ± 1.7</td>
<td>2.9 ± 1.3</td>
<td>2.0 ± 0.4</td>
</tr>
</tbody>
</table>

Data are mean ± SD; \(^aP<0.05, \(^bP<0.01\) compared with placebo; Abbreviations: AEA, N-arachidonoylethanolamine; Apo, Apolipoprotein; BDI-II, Beck Depression Inventory-II; BMI, Body mass index; BP, blood pressure; HbA1c, glycosylated haemoglobin A1c; HDL, high density lipoprotein; HOMA2-IR, homeostatic assessment model 2 - insulin resistance; LDL-C, low density lipoprotein cholesterol; NEFA, non-esterified fatty acid; OEA, oleoylethanolamine; OGTT, oral glucose tolerance test; PEA, palmitoylethanolamine; TG, triglyceride, UC, ultracentrifugation; VLDL, very low density lipoprotein; 2-AG, 2-arachidonoylglycerol