Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study

Diabetes Care 2016;39:1777–1786 | DOI: 10.2337/dc16-0650

OBJECTIVE
Cannabidiol (CBD) and Δ⁹-tetrahydrocannabivarin (THCV) are nonpsychoactive 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 randomized, double-blind, placebo-controlled study, 62 subjects with non-insulin-treated type 2 diabetes were randomized 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 end point was a change in HDL-cholesterol concentrations from baseline. Secondary/tertiary end points included changes in glycemic 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 end points were also evaluated.

RESULTS
Compared with placebo, THCV significantly decreased fasting plasma glucose (estimated treatment difference [ETD] = −1.2 mmol/L; P < 0.05) and improved pancreatic β-cell function (HOMA2 β-cell function [ETD = −44.51 points; P < 0.01]), adiponectin (ETD = −5.9 × 10⁶ pg/mL; P < 0.01), and apolipoprotein A (ETD = −6.02 μmol/L; P < 0.05), although plasma HDL was unaffected. Compared with 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 end points. CBD and THCV were well tolerated.

CONCLUSIONS
THCV could represent a new therapeutic agent in glycemic control in subjects with type 2 diabetes.
The endocannabinoid system (ECS) modulates food intake and energy homeostasis (1,2), and chronic overactivation of the ECS has been identified in obesity and type 2 diabetes (3). The ECS exerts some of its actions by 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 (HDL-C) 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 authorization 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 hyperglycemia, mainly through its anti-inflammatory and anti-oxidant properties (6–10). In animal models of obesity (ob/ob genetically obese mice), 4 weeks of treatment with CBD 3 mg/kg produced a 55% increase in HDL-C concentration and reduced total cholesterol by >25% (C.S., unpublished data). In addition, the same dose reduced liver TGs 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 Δ9-tetrahydrocannabinol (THC), CBD does not activate CB2 receptors in the brain and therefore lacks the psychotronic 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, the transient receptor potential vanilloid 1 (TRPV1) receptor, α1-adrenoceptors, μ opioid receptors, and the adenosine transporter and serotonin-1A receptors (14). CBD also activates and has physiological responses mediated by peroxisome proliferator–activated receptor γ (15–17). A CBD/THC combination (Sativex/Nabiximols; GW Pharmaceuticals) is currently licensed in most European Union 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; GW Pharmaceuticals) was granted orphan drug designation by the U.S. Food and Drug Administration 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 analog of THC, but with different pharmacological effects. It has been reported to behave as both a CB1/CB2 agonist and/or a CB1/CB2-neutral antagonist (20–24), probably dose-dependent, with agonism observed at high doses and antagonism at low doses (19). 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 (23) and transient receptor potential channels (24,25).

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 (26). The effect was similar to that of a CB1 antagonist, AM251, also used in the same study. In another study, involving diet-induced obese mice, oral THCV (2.5–12.5 mg/kg) reduced body fat content, increased energy expenditure, and reduced fasting insulin and 30-min insulin response to oral glucose tolerance test (OGTT) (27). In the same study, in genetically obese (ob/ob) mice, a similar increase in 24-h energy expenditure was observed with 3 mg/kg THCV, whereas 12.5 mg/kg THCV caused a significant reduction in liver TGs (27). In genetically obese mice (ob/ob), a 1:1 ratio of a combination of THCV and CBD (3:3 mg/kg) reduced change to 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 (C.S., unpublished data).

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 dyslipidemia and glycemic control in subjects with type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

**Subjects and Study Design**

This randomized, double-blind, placebo-controlled, parallel-group, phase IIa proof-of-concept study was conducted at four U.K. centers. The protocol was reviewed and approved by the East Midlands–Leicester Multi Centre Research Ethics Committee (10/H0406/42) and local research and development departments as required and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Subjects aged ≥18 years with type 2 diabetes and HbA1c ≤10% (86 mmol/mol), HDL-C ≥1.3 mmol/L in females and ≥1.2 mmol/L in males, and plasma TGs ≤10 mmol/L were eligible. Subjects needed to either receive no oral hypoglycemic agents or take stable doses of prescribed, noninsulin glucose-lowering therapies (metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, or glucagon-like peptide 1 [GLP-1] therapy) for 3 months prior to screening. Subjects not on statin therapy or on a stable dose of a statin for at least 4 weeks prior to randomization were eligible for inclusion. Subjects were also required not to make any changes to their diet or exercise for 4 weeks prior to randomization and during the course of the study.

Main exclusion criteria (see Supplementary Data for full details) included use of prohibited medications (insulin, fibrates, thiazolidinediones, therapeutic omega-3 fatty acids, and α-glucosidase inhibitors), recent or current use of cannabis, history of significant depression, planned travel outside the U.K. during the course of study, genetic dyslipidemia, or significant cardiac, renal, or hepatic impairment.

There was a 1- to 5-week period between screening (visit 1) and treatment randomization (visit 2). Visit 1 could be split into two separate visits (1A and 1B)
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 min before breakfast and 30 min before evening meal, typically 12 h apart for 13 weeks.

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

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

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

Plasma endocannabinoids N-arachidonoyl ethanolamine (AEA), 2-arachidonoylglycerol (2-AG), oleoyl ethanolamine (OEA), and palmitoylethanolamine (PEA) were analyzed using liquid chromatography-tandem mass spectrometry, based on a previously published method (28). Ketones, orexin A, and retinol-binding protein 4 (RBP-4) were analyzed using immunnoassay, whereas all other tertiary end points including adiponectin, resistin, leptin, E-selectin, vascular cell adhesion molecule, Vn Willebrand factor, C-reactive protein (CRP), interleukin-6, tumor necrosis factor-α, glucose-dependent insulinotropic peptide (GIP), ghrelin, and GLP-1 were analyzed by multiplex analysis, using commercially available kits (Milliplex, HMHMG-34K, HCVD1-67AK, HADK-1-61K-A, HCVD2-678K, BPHCVD05-6; Merck Millipore).

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

Adipose tissue distribution was assessed using whole-body MRE; images were analyzed by a blinded investigator using sliceomatic (TomoVision, Magog, Canada). Body weight and seven-point skinfold measures were also recorded. Hepatic TG concentration was assessed using MRS and analyzed using JMRUI software.

Patient’s Global Impression of Change (PGIC) and Clinician’s Global Impression of Change (CGIC) were assessed using an ordinal seven-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), in which 0 is no appetite (do not feel hungry) and 10 is maximum appetite (completely hungry all the time) (29). The change from mean baseline score (mean of 7 days before start of treatment) was compared with the mean score from the last 7 days on treatment (end of 13 weeks). Safety assessments included reporting for AEs and serious AEs (SAEs), recording vital signs, pre- and posttreatment laboratory sampling and electrocardiograms, 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 center, according to the randomization schedule. Study site staff identified the pack number to be dispensed to the subject at each of visits 2 and 3 according to the randomization schedule.

Analysis was performed using the intention-to-treat population; all subjects who were randomized 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% CIs were also calculated. The primary end point and the majority of secondary end points were analyzed using ANCOVA of the changes from baseline to the end of treatment in the associated parameter, with the exception of the PGIC and CGIC, which were analyzed 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 analyzed using ANCOVA with baseline value as covariate and treatment group and sex as factors or using pairwise Fisher 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 analyzed post hoc using a paired t test, and the glucose response to OGTT was analyzed using repeated-measures two-way ANOVA.

RESULTS
A total of 125 patients was screened and 62 randomized to the 5 treatment arms. The disposition of subjects enrolled is presented in Fig. 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 apolipoprotein A (Apo A) concentrations compared with placebo from baseline to the end of treatment (from 48.5 to 49.1 \( \text{mmol/L} \) in the THCV vs. 47.3 to 43.9 \( \text{mmol/L} \) in the placebo group; \( P < 0.05 \)) (Fig. 2A). THCV had no effect on LDL cholesterol (LDL-C) concentrations. CBD alone and in combination with THCV did not affect any of the lipid parameters (Table 2).

Glycemic Control
THCV reduced fasting plasma glucose concentration compared with placebo from baseline to the end of treatment (from 7.4 to 6.7 \( \text{mmol/L} \) in the THCV vs. 7.6 to 8.0 \( \text{mmol/L} \) in the placebo group; estimated treatment difference [ETD] = \(-1.24 \pm 0.6 \) [SEM]; \( P < 0.05 \)) (Fig. 3A). In line with this, there was a significant increase in HOMA2 \( \beta \)-cell function 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 \( \pm 16.1 \) [SEM]; \( P < 0.01 \)) (Table 2 and Fig. 3A). There was no significant difference in glucose response to OGTT at 2 h. However, when compared with baseline, THCV significantly improved 3-h blood glucose response (\( P < 0.05 \)) (Fig. 3C). CBD alone or in combination with THCV had no effect on glycemic parameters (Table 2).

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

Markers of Inflammation
Both THCV and CBD, or their combination, had no significant effect on plasma markers of inflammation (CRP, tumor necrosis factor-\( \alpha \), and interleukin-6) (Supplementary 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 favor of THCV treatment (ETD = \(-5.9 \times 10^3 \) 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 increase in the concentration of GIP (21.2 pg/mL; \( P < 0.05 \)) (Fig. 3C), without any effect on GLP-1 or ghrelin concentrations. Subjects taking a combination of CBD and THCV had no change in adipokine levels (Supplementary Table 1).

Body Weight
Baseline mean body weight (kg \( \pm SD \)) in the CBD, THCV, 1:1 CBD/THCV, 20:1 CBD/THCV, and placebo groups were 97.1 \( \pm 13.8 \), 98.3 \( \pm 17.5 \), 100.7 \( \pm 14.5 \), 100.5 \( \pm 17.9 \), and 94.2 \( \pm 19.1 \), respectively. There were no statistically significant changes in anthropometric parameters including weight, waist circumference, waist-to-hip ratio, and skinfold thickness in any of the treatment groups (Table 2).
An improvement in glucose response and Changes in HbA1c

Analyzing Glucose Response to OGTT

Post Hoc Analysis in THCV Group after 13 weeks of any treatment (Table 2).

There was no signiﬁcant change in the lev-

els of circulating AEA, 2-AG, OEA, and PEA
during the study. All other treatment-related AEs

were reported in individual subjects.

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 Supplementary Figs. 1 and 2. Analysis of these responses showed a treatment difference in favor 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 7 out of 11 (63.6%) patients in the CGIC on 1:1 CBD/THCV treatment, compared with only 2 of the 14 (14.3%) patients on placebo, with a reported 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 at 1 h and P < 0.01 at 3 h; n = 6) (Fig. 3D). In the same group of patients receiving diet/metformin only, compared with placebo, a signiﬁcant improvement in HbA1c was also observed (P < 0.05) (Fig. 3E).

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, and 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 the 20:1 CBD/THCV group experienced an AE of decreased appetite. Two subjects reported diarrhea with THCV, compared with 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 the study, and was not considered to be treatment related. One placebo patient experienced an SAE of myocardial ischemia 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). Although this remained in the “minimal depression” bracket, it was statistically signiﬁcant compared with 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 dyslipidemia. 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

Visceral Adiposity and Liver TGs

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

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

Analyzing Glucose Response to OGTT and Changes in HbA1c

An improvement in glucose response to OGTT was noted in the THCV group at 3 h (Fig. 3C). When subjects on any form of diabetes treatment other than diet/metformin were excluded from analysis, this effect became more pronounced (P < 0.05 at 1 h and P < 0.01 at 3 h; n = 13) (Fig. 3E). When subjects on any form of diabetes treatment other than diet/metformin were excluded from analysis, this effect became more pronounced (P < 0.05 at 1 h and P < 0.01 at 3 h; n = 6) (Fig. 3D). In the same group of patients receiving diet/metformin only, compared with placebo, a significant improvement in HbA1c was also observed (P < 0.05) (Fig. 3E).

Table 1—Summary of patient demographics and concomitant therapy

<table>
<thead>
<tr>
<th></th>
<th>CBD</th>
<th>THCV</th>
<th>1:1 CBD/THCV</th>
<th>20:1 CBD/THCV</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, number of subjects (%)</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 (%)</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>
<td>33.4 (7.0)</td>
<td>34.4 (5.8)</td>
</tr>
<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>
</tr>
<tr>
<td>Number (%) of patients on antidiabetic and lipid-lowering therapy</td>
<td>Metformin</td>
<td>9 (69)</td>
<td>9 (75)</td>
<td>10 (91)</td>
<td>11 (92)</td>
<td>12 (86)</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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

DPP-4, dipeptidyl peptidase 4.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBD (mmol/L)</strong></td>
<td>10.1 ± 0.2</td>
<td>10.2 ± 0.1</td>
</tr>
<tr>
<td><strong>THCV (mmol/L)</strong></td>
<td>4.5 ± 0.3</td>
<td>4.6 ± 0.2</td>
</tr>
<tr>
<td><strong>Total-C (mmol/L)</strong></td>
<td>3.1 ± 0.1</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td><strong>LDL-C (mmol/L)</strong></td>
<td>2.5 ± 0.3</td>
<td>2.6 ± 0.4</td>
</tr>
<tr>
<td><strong>HDL-C (mmol/L)</strong></td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td><strong>Liver TG (%)</strong></td>
<td>26.9 ± 6.9</td>
<td>27.1 ± 7.1</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>33.2 ± 5.4</td>
<td>33.0 ± 4.9</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>107.7 ± 3.5</td>
<td>108.0 ± 3.6</td>
</tr>
<tr>
<td><strong>Waist-to-hip ratio</strong></td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td><strong>HOMA2-IR</strong></td>
<td>2.3 ± 1.0</td>
<td>2.4 ± 1.1</td>
</tr>
<tr>
<td><strong>HOMA2 b-cell function</strong></td>
<td>70.9 ± 3.5</td>
<td>71.0 ± 3.6</td>
</tr>
<tr>
<td><strong>2-AG (nmol/L)</strong></td>
<td>5.0 ± 1.1</td>
<td>5.1 ± 1.2</td>
</tr>
<tr>
<td><strong>PEA (mg/L)</strong></td>
<td>2.7 ± 0.6</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td><strong>C-peptide (nmol/L)</strong></td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td><strong>Apo B/Apo A ratio</strong></td>
<td>3.1 ± 0.2</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td><strong>HOMA2-IR</strong></td>
<td>2.3 ± 1.0</td>
<td>2.4 ± 1.1</td>
</tr>
<tr>
<td><strong>HOMA2 b-cell function</strong></td>
<td>70.9 ± 3.5</td>
<td>71.0 ± 3.6</td>
</tr>
<tr>
<td><strong>2-AG (nmol/L)</strong></td>
<td>5.0 ± 1.1</td>
<td>5.1 ± 1.2</td>
</tr>
<tr>
<td><strong>PEA (mg/L)</strong></td>
<td>2.7 ± 0.6</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td><strong>C-peptide (nmol/L)</strong></td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td><strong>Apo B/Apo A ratio</strong></td>
<td>3.1 ± 0.2</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Apo A, apolipoprotein A; Apo B, apolipoprotein B; BP, blood pressure; HOMA2-IR, HOMA2 insulin resistance; NEFA, nonesterified fatty acid; Total-C, total cholesterol; UC, ultracentrifugation; *p < 0.05; **p < 0.01 compared with placebo.
agent for glycemic control in subjects with type 2 diabetes.

The ECS plays an important role in modulating energy intake and expenditure (for reviews, see Refs. 1,2), and a chronically overactive 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 favorable 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 tonelike obesity, because of its conditions of increased endocannabinoid signaling ($\text{THCV}$) may act as a functional antagonist in $\text{CBD}$ caused a significant reduction in resistin ($\text{C}2$) and an increase in GIP concentration ($\text{D}$), when compared with pretreatment values. Data were analyzed post hoc using paired t test and presented as mean ± SEM. BID, twice daily. *$P < 0.05$; **$P < 0.01$.

Figure 2—Compared with placebo, THCV alone caused a significant improvement in the concentration of Apo A ($\text{A}$) and adiponectin ($\text{B}$). Data were analyzed by ANCOVA and presented as mean ± SEM. CBD caused a significant reduction in resistin ($\text{C}$) and an increase in GIP concentration ($\text{D}$), when compared with pretreatment values. Data were analyzed post hoc using paired t test and presented as mean ± SEM. BID, twice daily. *$P < 0.05$; **$P < 0.01$.

**Figure 2**—Compared with placebo, THCV alone caused a significant improvement in the concentration of Apo A ($\text{A}$) and adiponectin ($\text{B}$). Data were analyzed by ANCOVA and presented as mean ± SEM. CBD caused a significant reduction in resistin ($\text{C}$) and an increase in GIP concentration ($\text{D}$), when compared with pretreatment values. Data were analyzed post hoc using paired t test and presented as mean ± SEM. BID, twice daily. *$P < 0.05$; **$P < 0.01$.

**Figure 2**—Compared with placebo, THCV alone caused a significant improvement in the concentration of Apo A ($\text{A}$) and adiponectin ($\text{B}$). Data were analyzed by ANCOVA and presented as mean ± SEM. CBD caused a significant reduction in resistin ($\text{C}$) and an increase in GIP concentration ($\text{D}$), when compared with pretreatment values. Data were analyzed post hoc using paired t test and presented as mean ± SEM. BID, twice daily. *$P < 0.05$; **$P < 0.01$. **Figure 2**—Compared with placebo, THCV alone caused a significant improvement in the concentration of Apo A ($\text{A}$) and adiponectin ($\text{B}$). Data were analyzed by ANCOVA and presented as mean ± SEM. CBD caused a significant reduction in resistin ($\text{C}$) and an increase in GIP concentration ($\text{D}$), when compared with pretreatment values. Data were analyzed post hoc using paired t test and presented as mean ± SEM. BID, twice daily. *$P < 0.05$; **$P < 0.01$.
Moreover, rimonabant improved the lipid profile (increased HDL-C and reduced TG levels), whereas THCV had no effect on lipid parameters in our study (4). 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 and monoacyl glycerol lipase, thereby inhibiting the hydrolysis of AEA and 2-AG, respectively (40). THCV, therefore, can act as an indirect agonist at the cannabinoid receptors, by enhancing the activity of the ECS. Because 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 ECS. Recent animal data from Wargent et al. (27) 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 with this, the dose used on our study (10 mg/day, 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 (41). 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 (42). Despite having positive effects on resistin and GIP, CBD did not produce any improvement in glycemic control.

CBD is known for its indirect agonism at the CB1 receptors, by either increasing CB1 constitutional activity or the endocannabinoid tone. CBD has been reported to inhibit hydrolysis of AEA by fatty acid amide hydrolase (but only at high micromolar levels) and also increases 2-AG levels (39). In a recent clinical study, in subjects with schizophrenia, 800 mg/day

---

**Figure 3**—Compared with placebo, THCV alone caused significant improvement in fasting glucose (A), and in keeping with this, there was a highly significant improvement in β-cell function measured by HOMA2 (B). THCV caused significant improvement in 3-h glucose response during OGTT (C), when compared with pretreatment values. Data were analyzed using two-way ANOVA and presented as mean ± SEM. D: Compared with pretreatment values, there was a highly significant improvement in 3-h glucose response to OGTT with THCV, when subjects on any oral hypoglycemic therapy other than diet and/or metformin were excluded from analysis (n = 6). In the same subgroup (analyzed post hoc), compared with placebo, there was a statistically significant improvement in Hba1c (E). Data were analyzed post hoc using repeated-measures two-way ANOVA and paired t test, respectively, and presented as mean ± SEM. BID, twice daily. *P < 0.05; **P < 0.01.
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 ECS at the doses investigated.

Studies 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 (7–9). In a 70-kg individual, a 20 mg/kg/day dose equates to 1,400 mg/day. Similarly, human studies have used CBD in higher doses (12,43). The dose used in our study was 200 mg/day, which could possibly explain lack of therapeutically significant 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 toward 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. Although the combination of CBD and THCV did not produce any favorable effects on any of the parameters, the favorable 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 of the treatment groups. There were no reports of depression and no clinically significant abnormalities on electrocardiogram and laboratory results, including blood count and liver and renal biochemistry, in any treatment groups. There was one SAE of myocardial ischemia 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, although 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.

**CONCLUSIONS**

In this clinical study, the first to study the effects of CBD and THCV in subjects with type 2 diabetes and dyslipidemia, THCV improved glycemic 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.

**Acknowledgments.** The authors thank Lesley Taylor and Heather Lauder of GW Pharmaceuticals for help with preparing the manuscript.

**Funding.** This study was supported by GW Research Ltd.

**Duality of Interest.** S.H.R. has been a member of GW Pharmaceutical’s Speaker’s Board and has received funding for clinical studies. G.D.T. is supported by the National Institute for Health Research Oxford Biomedical Research Centre Programme. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** K.A.J. was involved in study design, researched data, wrote the manuscript, and reviewed and edited the manuscript. S.H.R. recruited patients and reviewed and edited the manuscript. D.A.B. and J.O.B. researched data and reviewed and edited the manuscript. E.L.T. researched data. C.S. was involved in study design and reviewed and edited the manuscript. S.E.O. was involved in study design, wrote the manuscript, and reviewed and edited the manuscript. G.D.T. was involved in study design, served as chief investigator, wrote the manuscript, and reviewed and edited the manuscript. C.S. 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.

**References**

8. Toth CC, Jedrezewski NM, Ellis CL, Frey WH. Cannabidiol-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. Mol Pain 2010;6:16
13. Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res 2011;130:216–221
through the control of neuroimmune axis. PLoS One 2011;6:e28159
18. Thomas A, Stevenson LA, Wease KN, et al. Evidence that the plant cannabinoid Delta9-
tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist. Br J Pharmacol 2005;
146:917–926
19. Pertwee RG, Thomas A, Stevenson LA, et al. The psychoactive plant cannabinoid, Delta9-
tiform and in vivo seizure activity in adult rats. Epilepsia 2010;51:1522–1532
22. Bátkaï S, Mukhopadhyay P, Horváth B, et al. Δ8-Tetrahydrocannabinol prevents hepatic is-
plant-derived cannabinoid receptor antagonists show hypoglycemic properties in fasted and non-
27. Wargent ET, Zaib MS, Silvestri C, et al. The cannabinoid Δ9-tetrahydrocannabinol (THCV)
ameliorates insulin sensitivity in two mouse models of obesity. Nutr Diabetes 2013;3:a68
28. Richardson D, Ortori CA, Chapman V, Kendall DA, Barrett DA. Quantitative profiling of endocannabinoids and related compounds in rat brain using liquid chromatography-
30. Endler NS, Rutherford A, Denisoff E. Beck depression inventory: exploring its dimension-
31. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and
betic mice. Autoimmunity 2006;39:143–151
inflammatory activity of cannabidiol, a non-
vide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Par-
37. Barter PJ. Hugh Sinclair lecture: the regula-
39. Whitehead JP, Richards AA, Hickman UJ, MacDonald GA, Prins JB. Adiponectin—a key adi-
pokine in the metabolic syndrome. Diabetes Obes Metab 2006;8:264–280
40. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabinoid and Δ9-
42. Irwin N, Flatt PR. Evidence for beneficial effects of compromised gastric inhibitory poly-
peptide action in obesity-related diabetes and possible therapeutic implications. Diabetologia 2009;52:1724–1731