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Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial

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Abstract
Adults with ADHD describe self-medicating with cannabis, with some reporting a preference for cannabis over ADHD medications. A small number of psychiatrists in the US prescribe cannabis medication for ADHD, despite there being no evidence from randomised controlled studies. The EMA-C trial (Experimental Medicine in ADHD-Cannabinoids) was a pilot randomised placebo-controlled experimental study of a cannabinoid medication, Sativex Oromucosal Spray, in 30 adults with ADHD. The primary outcome was cognitive performance and activity level using the QbTest. Secondary outcomes included ADHD and emotional lability (EL) symptoms. From 17.07.14 to 18.06.15, 30 participants were randomly assigned to the active (n=15) or placebo (n=15) group. For the primary outcome, no significant difference was found in the ITT analysis although the overall pattern of scores was such that the active group usually had scores that were better than the placebo group (Est=−0.17, 95%CI-0.40 to 0.07, p=0.16, n=15/11 active/placebo). For secondary outcomes Sativex was associated with a nominally significant improvement in hyperactivity/impulsivity (p=0.03) and a cognitive measure of inhibition (p=0.05), and a trend towards improvement for inattention (p=0.10) and EL (p=0.11). Per-protocol effects were higher. Results did not meet significance following adjustment for multiple testing. One serious (muscular seizures/spasms) and three mild adverse events occurred in the active group and one serious (cardiovascular problems) adverse event in the placebo group. Adults with ADHD may represent a subgroup of individuals who experience a reduction of symptoms and no cognitive impairments following cannabinoid use. While not definitive, this study

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provides preliminary evidence supporting the self-medication theory of cannabis use in ADHD and the need for further studies of the endocannabinoid system in ADHD.
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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects around 5% of children and 3% of adults (Polanczyk et al., 2007; Simon et al., 2009). The disorder is characterised by developmentally inappropriate and impairing levels of inattention, hyperactivity and impulsivity, commonly accompanied by emotional dysregulation, cognitive impairments and psychiatric comorbidities (Asherson et al., 2016).

One of the most common problems associated with ADHD is co-occurring substance abuse (Gudjonsson et al., 2012; Lee et al., 2011; Young and Thome, 2011). One theory posited to explain the increased risk of substance use in ADHD is that of self-medication (Bolea-Alamañac et al., 2014; Loflin et al., 2014). There are several potential points that underpin the self-medication hypothesis for substance abuse in ADHD. First, different motivations behind drug use have been reported. ADHD cases were more likely to use drugs to improve their mood and sleep, whereas those without ADHD for 'getting high' (Horner and Scheibe, 1997; Wilens, 2004), suggesting that drug use in ADHD could help to improve symptoms. Secondly, stimulant medications are the recommended first line treatment in ADHD and, alongside cannabis, stimulants are one of the most common classes of drugs of abuse in ADHD (Biederman et al., 1995; Dennis et al., 2004; Gudjonsson et al., 2012; Huntley et al., 2012). This might indicate that individuals with ADHD are more likely to use drugs that alleviate symptoms of the disorder. Thirdly, in clinical practice, it is not uncommon for adults with ADHD to report potential benefits from the use of cannabis. Descriptions of cannabis effects by ADHD patients include feeling calmer, less restless and improved sleep, while a few report that cannabis helps them to remain focused (Asherson, personal communication; Milz and Grotenhermen, 2015). One case study of adult ADHD reported improved driving skills after smoking cannabis (Strohbeck-kuehner et al., 2008), and anecdotal accounts also abound on the internet. Analysis of online forums where ADHD and cannabis use was discussed found three-times as many comments advocating for the therapeutic (as opposed to harmful) effects of cannabis on ADHD (Mitchell et al., 2016). In the US, medical professionals advocated for cannabis as a treatment for ADHD before a congressional subcommittee on drug policy (Marijuana and Medicine, U.S. House of Representatives, 2004), and a small number of clinicians prescribe or recommend medical cannabis to treat ADHD (Marijuana and Medicine, U.S. House of Representatives, 2004).

Investigating the effects of cannabinoids in ADHD may therefore shed light on the high use of cannabis among adults with ADHD. Investigations of new pharmacological targets for ADHD are also important as these may lead to the discovery of novel mechanisms underpinning the disorder and potentially the development of new treatments. In ADHD there are already effective treatments such as stimulants and atomoxetine, however these are not always effective, partial response is common and they are not always well tolerated (Bolea-Alamañac et al., 2014; Faraone et al., 2015; Leonard et al., 2004; Sangal et al., 2006). In some cases more severe adverse effects have been reported, leading to the US Food and Drug Administration (FDA) approved treatments for ADHD to carry warnings that their use could involve risks of cardiovascular effects, growth suppression and the development of psychosis or other psychiatric conditions (FDA, 2006).

Previous studies report that impairments in cognitive measures of cortical control and arousal (e.g. increased omission[1] and commission[2] errors and slowed reaction times during sustained attention and inhibition tasks) are related to cannabis use (McDonald et al., 2003; Ramaekers et al., 2009, 2006; Umut et al., 2016). However, this may not be consistent with the subjective accounts of patients with ADHD, who could represent a subgroup that responds more positively to cannabinoids. For example, one study found that cognitive impairment in adulthood was associated with a childhood diagnosis of ADHD, but not cannabis use in adulthood (Tamm et al., 2014).

The mechanism for any potential therapeutic effects of cannabinoids in ADHD is unknown. One possibility is that cannabinoids enhance dopaminergic transmission (Bossong et al., 2015, 2009; Voruganti et al., 2001), which is thought to be the main mechanism by which stimulants decrease ADHD symptoms and improve cognitive performance (Leonard et al., 2004). However, the enhancement of dopamine following cannabis use is not a consistent finding (Barkus et al., 2011; Stokes et al., 2009) and other mechanisms could be involved.

Despite interest in the effects of cannabis in ADHD and the prescription or recommendation of cannabis to treat ADHD by a small number of clinicians in the US, there has yet to be an experimental investigation of cannabinoids in ADHD. We therefore set out to conduct a pilot study of a cannabinoid medication in adults with ADHD, to provide an initial evaluation of the potential effects on cognitive impairment and behavioural symptoms.

2. Experimental procedures

2.1. Study design

The Experimental Medicine in ADHD-Cannabinoids (EMA-C) study was a single centre, 6-week, double-blind, randomised placebo-controlled experimental trial of Sativex Oromucosal Spray, a cannabinoid medication containing a 1:1 ratio of delta-9-tetrahydrocannabinol (Δ9-THC) to cannabidiol (CBD). The study was conducted at the Social Genetic and Developmental Psychiatry (SGDP) centre, Institute of Psychiatry Psychology and Neuroscience, King's College London, in conjunction with the South London and the

[1]Where a participant fails to respond where a response is required during a cognitive task.

[2]Where a participant responds when a response is not required during a cognitive task.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
18-55 years of age.	
Diagnosis of combined type ADHD in accordance with DSM-5.	Current/primary diagnosis of: ASD, recurrent major depression, panic/anxiety disorder, bipolar I disorder, any psychotic disorder, OCD, tourette's, general learning difficulties (IQ<70), neurological problems, known/suspected history of drug/alcohol dependence.
At baseline a score of >24 on the 18-item Conners' Adult ADHD Rating Scale (CAARS) (Conners et al., 1999).	First degree relative with a psychotic disorder.
Unmedicated/medicated with stimulants only and willing to come off this medication for 1 week before and for the (6 week) duration of the study.	Use of non-stimulant ADHD medication.
Willing to not use any prescription/non-prescription/recreational drugs during the study.	Use of cannabis/cannabis-based medications in the 30-day period prior to study entry. Concurrent history of renal, hepatic, cardiovascular or convulsive disorders. Females who were pregnant or breastfeeding Female participants of child bearing potential, and male subjects whose partner was of child bearing potential, who were unwilling to ensure that they or their partner used two effective forms of contraception (e.g. oral contraception, double barrier, intra-uterine device) during the study and for three months thereafter[a]

Note. ASD=Autism Spectrum Disorder; OCD=Obsessive Compulsive Disorder.
[a]This is because there is not enough information to say that Sativex is safe in pregnancy.

Maudsley NHS Foundation Trust. Research ethics was approved by the National Research Ethics Service Committee-London Bridge (reference: 14/LO/0606). The Medicines and Healthcare Regulatory Products Agency classified the protocol as an experimental design that did not require MHRA authorisation.

2.2. Changes to trial design

The protocol included outcomes at 3 time-points (baseline; 2-weeks; and 6-weeks). Participants attended the SGDP Centre for their baseline and 6-week assessments. For the 2-week assessment, participants were provided with questionnaires and a stamped addressed envelope and asked to complete and post these back to us. However, only 16 out of 30 participants completed this. Therefore the 2-week assessment was dropped from the analysis.

2.3. Participants

Between 17th July 2014 and 21st May 2015, 233 adults were assessed for eligibility. The inclusion/exclusion criteria are shown in Table 1. Criteria included a diagnosis of combined type ADHD in accordance with DSM-5 (assessed using the Diagnostic Interview for ADHD in Adults (DIVA)) which asks about the presence of ADHD symptoms in both childhood and adulthood (Kooij and Francken, 2010) and a baseline score of >24 on the 18-item Conners' Adult ADHD Rating Scale (CAARS) (Conners et al., 1999). Participants were unmedicated with any psychoactive drug treatment, or medicated with stimulants only and were willing to come off this medication for one week before and for the six week duration of the study. Written informed consent was provided by all participants. Following review by a consultant psychiatrist (PA), 30 adults with ADHD were randomised to the treatment arms and included in the intention to treat (ITT) analysis (Figure 1).

2.4. Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to the active Sativex or placebo groups. The randomisation list was generated by an independent statistician who produced a treatment allocation schedule to two equal-sized blocks (treatment and placebo) at random via a random number generator in the R statistical package (using the sample.int() function). The randomisation list was sent to the hospital pharmacy where the medication was labelled and blinded before being dispensed. The allocation sequence was concealed from the researchers in sequentially numbered, opaque, sealed envelopes which were kept by the independent statistician in a locked drawer in the SGDP Centre. Neither the statistician who produced the randomisation schedule nor the pharmacist who labelled and blinded the medication were involved in any other aspect of the study. Emergency unblinding was possible with 24 h access to a mobile phone number (provided to the participants and pharmacists) with a member of the research team and to a trained clinician (PA or REC). Both investigators and participants were blind to treatment allocation. The placebo and active treatments were identical in appearance and method of administration (oromucosal sprays) and were flavoured with peppermint. Post-intervention, participants were asked which group they thought they were allocated to. These estimates were used to assess the maintenance of blinding. Treatment status was unblinded only after all data had been collected and cleaned (the final cleaned anonymised datafile was dated, stored and sent to colleagues unrelated to the trial prior to unblinding).

2.5. Procedures

2.5.1. Intervention

The active treatment was Sativex Oromucosal Spray (GW Pharma Ltd., Salisbury. UK). Each 100 microlitre spray contains 2.7 mg delta-9-tetrahydrocannabinol (Δ9-THC) and 2.5 mg cannabidiol

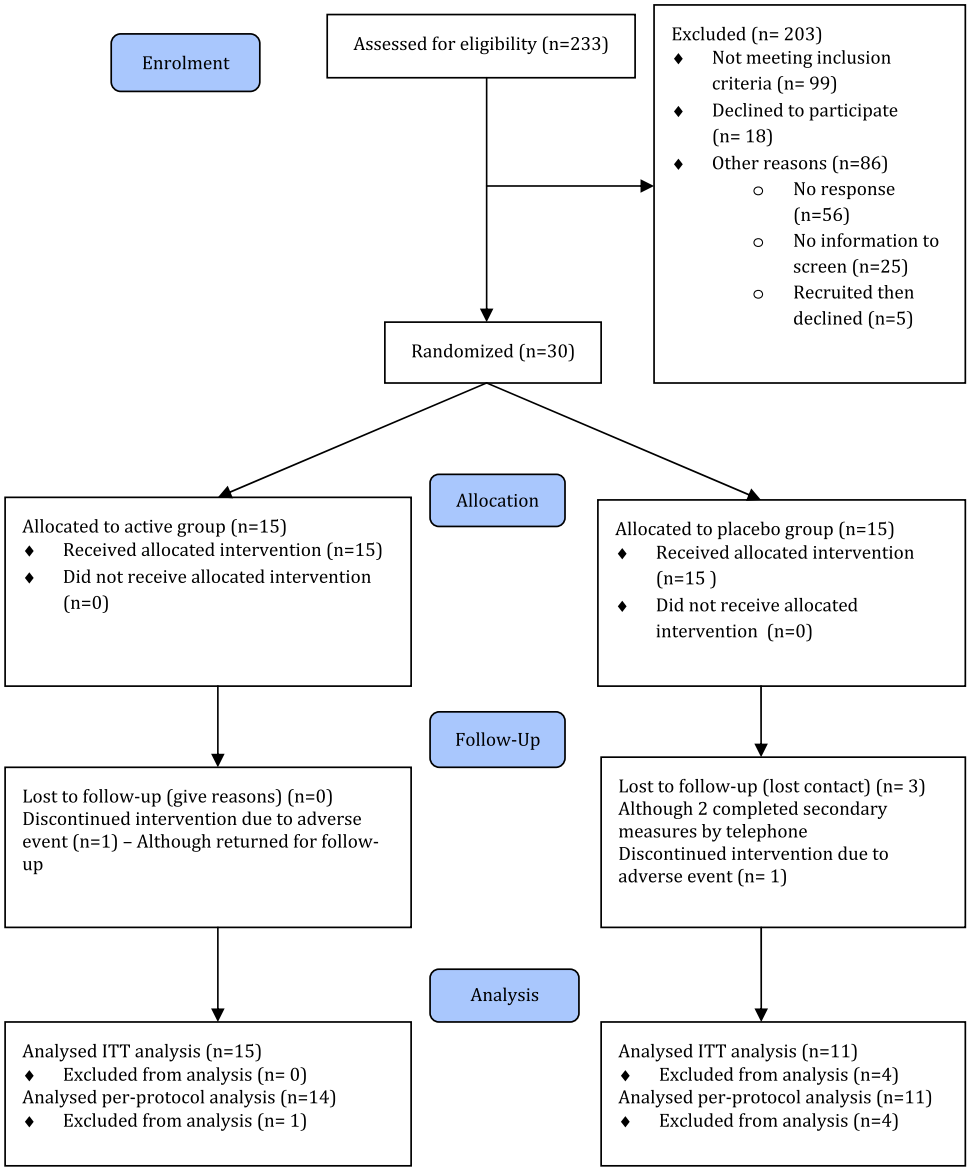

Figure 1 CONSORT flow diagram for the EMA-C trial.

(CBD). Placebo treatment contained ethanol, propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavouring and colourings. Both the Sativex and placebo appeared identical and were flavoured with peppermint. The treatments were stored and dispensed by the Maudsley Hospital pharmacy following prescriptions by one of two qualified psychiatrists (PA or Dr Céline Ryckaert). Patients currently treated with stimulants were asked to stop their medication for 1 week before their baseline assessments and for the duration of the study. Patients on long-acting medications, such as atomoxetine, were excluded from the study.

2.5.2. Titration period, dosing and safety monitoring

All participants in both arms of the study underwent a two week titration period, after which they continued at the final optimal dose. At the end of the baseline assessment they received a 'dosing diary'. The diary contained titration and dosing instructions and asked the participant to record the number of sprays taken each day (See Supplementary Text S1). The two week titration period was conducted according to a dosing schedule (advised by GW Pharma) whereby treatment was increased daily (See Table S1). The maximum dose for the study was 14 sprays per day. During the titration and remaining 4-week period safety monitoring and evaluation of the effects of the spray were carried out on days 4, 8, 12, 14 and 28. On these days participants were called by a researcher and asked to complete a standard side-effect rating scale, the 18-item Conners' Adult ADHD Rating Scale (Conners et al., 1999), and general questions regarding their current dosage and whether they were finding any effects or adverse effects from the treatment. If in the opinion of the participant or the investigators, there were minor adverse effects that could be exacerbated at a higher dose, the participant was advised to either stay at the dose they were at or reduce to a lower dose. Titration upwards was also stopped if all ADHD symptoms were scored as negligible or absent (score of 0 or 1 on all items of the CAARS). Participants were advised to spread the doses out throughout the day as best suited them, taking into account any minor adverse events, symptom score on the CAARS, and the length of time the effect from each spray lasted. On day 14 it was decided between the participant and the investigator as to the optimal dose for them to continue for the remaining four weeks of the trial. Those who did not report effects from the spray were advised to titrate up to the maximum dosage and then continue at a dose they felt they could manage to take for the

remainder of the study. PA oversaw this process and managed any queries or concerns as required.

2.5.3. Alteration to titration period and dosing

After the first 3 participants had begun the trial it became clear that the titration schedule advised by GW Pharma was too high for adults with ADHD participating in the study. This is most likely because the recommended schedule for use of Sativex was based on efficacy and safety data for the symptom relief of multiple sclerosis, for which Sativex is licensed. We therefore altered the protocol by informing participants at the end of the baseline session that for some people the titration schedule was too high, and that if they found an effect from the medication they should not take another dose until that effect had started to wear off. The close monitoring of participants during the titration period ensured participants remained aware of this and that the titration process was individualised to the reported response from each patient.

2.5.4. Assessments

Baseline assessments were conducted at the SGDP centre, followed by randomisation on the same day. Trial medication was started the following morning. Participants underwent the 2 week titration period, before continuing on the optimised dose for a further 4 weeks. Primary and secondary outcomes were assessed at baseline (day 1) and 42 days post-randomisation[3] (Figure S1). For the day 42 outcome assessment, participants were asked to take a dose of their study medication as soon as they arrived at the appointment. Assessment for the primary outcome occurred 1 hour after dosing.

2.5.5. Outcomes

The primary endpoint was cognitive performance and activity level (head movements) measured using the Quantitative Behavioural Test (QbTest) (Iberstadt, 2012). The QbTest is a 20 min, continuous performance test which is used to measure cognitive performance related to sustained attention and response inhibition, as well as motor restlessness. During the test four different stimuli (red and blue squares; red and blue circles) are presented in a random order. If a stimulus matches the previous stimulus it is a target, otherwise it is a non-target. In total 600 stimuli are shown at a 25% target ratio. The participant is asked to respond to a target by pressing a clicker and to inhibit responses to non-targets. During the test head movements are measured by means of a high-resolution motion tracking system that consists of an infra-red camera and a reflector attached to the participant's headband. Outcome measures are calculated per test quartile, each representing five minutes of the test duration. The first quartile is not taken into account in the outcome measures because it is less strongly associated with ADHD. Three cardinal outcomes are computed as Q-scores (standard deviations from the average result of an age and gender adjusted norm group): QbInattention,[4] QbActivity,[5] and QbImpulsivity.[6] The primary outcome was the mean of these three outcomes, a measure that has been found previously to be sensitive to medication effects in adults with ADHD (Bijlenga et al., 2015). A Q-score ≥ 1.5 is considered an atypical result. Further individual analyses were conducted for activity, % commission errors (CE)[6], % omission errors (OE)[4] and reaction time variability (RTV).

Secondary outcomes included investigator rated ADHD symptoms using the Conners Adult ADHD Rating Scale (CAARS) (Conners et al., 1999) and emotional dysregulation using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADS) (Wender, 1995). Cognitive performance was further measured using the Sustained Attention to Response Task (SART) (O'Connell et al., 2009), a computerised go/no-go task measuring response inhibition and sustained attention. Self-report rating scales included emotional lability using the Centre for Neurologic Study Lability Scale (CNS-LS) (Moore et al., 1997) and Affective Lability Scale-Short Form (ALS-SF) (Oliver and Simons, 2004), and functional impairment using the Weiss Functional Impairment Rating Scale Self Report (WFIRS-S) (Weiss, 2007).

Safety measures included a full medical history, history of cannabis use with no adverse effects, and vital signs and frequent safety monitoring during the study. For safety monitoring, participants were called on days 4, 8, 12, 14 and 28 and asked to complete a standard side-effect rating scale, the 18-item Conners' Adult ADHD Rating Scale (Conners et al., 1999), and general questions regarding whether they were finding any effects/adverse effects from the treatment. If in the opinion of the participant or the investigators, there were minor adverse effects that could be exacerbated at a higher dose, the participant was advised to either stay at the dose they were at or reduce to a lower dose. Participants were provided with a 'study card' which stated they were taking part in a trial and contained contact details, including 24-h emergency phone numbers held by PA and Dr Ryckaert.

2.6. Statistical analyses

30 participants were randomised, providing 80% power to detect a large Cohen's *d* effect size of 1.06 (26% power to detect a moderate effect ($d=0.5$) and 8% power to detect a small effect ($d=0.02$)), at a significance level of 0.05. Although large effects are unlikely, with estimated effects of stimulants around 0.6 for RTV and 0.4 for measures of response inhibition (Coghill et al., 2014), the sample size was considered sufficient for the first ever evaluation of Sativex in ADHD, which aimed to assess feasibility and potential effect sizes, necessary to inform a larger, definitive trial (Craig et al., 2008).

The intent-to-treat (ITT) analysis, considered the primary analysis, included every participant who was randomised. The per-protocol analysis, considered the secondary analysis, included only those patients who adhered to the protocol for trial duration (Lewis and Machin, 1993). The primary ITT analysis was based on a repeated measures linear model that included: GROUP, TIME and a GROUP $\times$ TIME interaction term as fixed effects, with an unstructured covariance matrix of intra-patient covariance between time-points (Kincaid, 2005). Effect sizes were classed as the estimated (Est) slope difference between the two treatment groups, from baseline to follow-up. Sensitivity analyses assessed the influence of missing data through multiple imputation under the Missing At Random (MAR) and Missing Not At Random (MNAR) assumptions. All reported *p*-values are two-sided, and all CIs are 95%. A nominal significance level of $p=0.05$ was used, with adjustment for multiple testing applied to secondary outcomes (the Bonferroni-Holm method adjusted for 13 statistical tests). Given this was a pilot study we also highlight trends ($p \leq 0.10$) towards treatment effects. Analyses were performed using SAS, version 9.4, baseline comparisons were carried out using STATA, version 11.

Given this was a pilot experimental study a data monitoring committee was not established. The study was coordinated on a

[3] 6 weeks was chosen in line with the duration of previous RCTs of Sativex in patients with Multiple Sclerosis; or who had neuropathic pain, which found efficacy of Sativex after 5–6 weeks (e.g. Nurmikko et al., 2007) (there are no studies of Sativex in adults with ADHD therefore trial duration could not be based on RCTs in this population).

[4] Combining omission errors (OE: where a participant fails to respond when a response is required), mean reaction (RT) time for correct responses and reaction time variability (RTV: the standard deviation of RTs).

[5] Combining time active, distance, area, and micro-events (small movements of the reflective marker).

[6] Combining commission errors (CE: where a participant responds where a response is not required) and normalized CE.

Table 2 Baseline demographics.

	N: A/P	Active: M(SD)/N	Placebo: M(SD)/N
Age (y/m)	15/15	36.91 (11.70)	38.90 (11.54)
Sex (f/m)	15/15	6/9	5/10
IQ	15/15	111.87 (12.59)	114.93 (14.79)
Medication (med/unmed)	15/15	8/7	7/8
Income (£)	12/12	32,257.75 (26,461.55)	32,635.67 (42,998.28)
Employment status			
Employed	15/15	14	9
Unemployed*	15/15	0	5
Full-time student	15/15	1	1
Highest level of education			
No qualifications	15/14	1	0
GCSE/Vocational*	15/14	1	6
AS-Level/A-Level	15/14	3	1
Degree (undergrad/ postgrad)	15/14	10	7
$\geq$ 1 comorbid condition (MINI)	15/15	10	12
Cannabis use			
No use	15/15	5	5
Daily (present)[a]	15/15	3	1
Daily (past)[a]	15/15	1	3
Weekly (past)	15/15	1	0
Monthly (present)	15/15	0	1
Monthly (past)	15/15	3	3
Yearly (past)	15/15	2	2
Primary endpoint			
QbTest	14/14	1.73 (0.66)	1.71 (0.95)
QbTest: individual endpoints			
Qb Activity	14/14	2.66 (0.79)	2.61 (0.87)
Qb CE (%)	14/14	1.9 (2.48)	1.36 (1.35)
Qb OE (%)	14/14	22.74 (15.22)	26.34 (21.13)
Qb RTV (ms)	14/14	210.79 (59.02)	198.0 (85.06)
Secondary outcomes			
ADHD symptoms			
CW Inattention	15/15	27.27 (4.42)	27.33 (6.17)
CW Hyp/Imp	15/15	19.4 (4.24)	19 (7.44)
CW EL	15/15	15.6 (5.53)	19.07 (6.26)
Cognition			
SART CE	15/14	36.53 (16.24)	32.71 (16.55)
SART OE	15/14	51.8 (53.67)	41 (53.10)
SART RTV	15/14	186.85 (51.56)	156.32 (59.88)
Emotional lability			
CNS-LS	15/15	30.67 (15.43)	30.2 (16.95)
ALS	15/15	22.33 (11.14)	22.2 (9.51)
Functional impairment			
WFIRS Total	15/15	1.17 (0.52)	1.11 (0.33)

Note. N A/P=number of participants in the active/placebo group, y/m=years/months, f/m=female/male, OE=omission errors, CE=commission errors, RTV=reaction time variability.

*$p<0.05$.

[a]Daily as defined as $\geq$ use on 4 days per week.

daily basis by REC, EW and PA. This trial is registered at clinicaltrials.gov (number: NCT02249299).

3. Results

Between 17th July 2014 to 21st May 2015, 233 patients were screened and 109 were eligible, of whom 30 were enrolled and randomised (Figure 1). Of these, 1 participant in the active and 1 in the placebo group failed to complete the QbTest because they could not tolerate the task. Due to technical difficulties 2 participants in the placebo group (1 at baseline, 1 at follow-up) could not complete the SART. In the placebo group complete follow-up data were not obtained from 2 participants: 1 experienced an adverse event resulting in complete withdrawal and contact was lost with the second. Partial follow-up data were obtained from 2 other participants: 1 had a head injury and the second, logistical problems. These 2 participants failed to return for follow-up, but completed the CAARS/WRAADS, CNS-LS and ALS-SF over the telephone. In the active group, 1 participant experienced an adverse event 2 weeks into the trial and stopped taking the study medication, but attended their follow-up assessment session as scheduled. Therefore for the primary outcome, the ITT analysis included 15 participants in the active and 11 in the placebo group. The per-protocol analysis included 14 participants in the active and 11 in the placebo group. Patient demographics across the active and placebo groups were similar, including current daily (~4 days p/week) cannabis use ($N=3$ active, $N=1$ placebo) (Table 2).

The ITT analysis is shown in Table 3, the per-protocol analysis is shown in Table S3 and adjustment for multiple testing is shown in Table S4. The primary endpoint, performance on the QbTest, showed no statistically significant differences between the groups, although the overall pattern of findings was such that the active group generally had scores that were better than the placebo group ($F_{1,28}=2.04$, $p=0.16$), with an estimated (Est) reduction in scores of 0.17 (95% CI −0.40 to 0.07) in the active compared with placebo, from baseline to follow-up. This improvement in QbTest score was greater in the per-protocol analysis which showed an improvement at trend level ($F_{1,23}=4.01$, $p=0.06$) in the active group, with an estimated reduction of 0.24 (95% CI −0.48 to 0.01).

Analysis of the individual endpoints on the QbTest showed, for the active group, a nominally significant reduction in commission errors ($F_{1,28}=4.29$, $p=0.05$, Est = −0.81, 95% CI −1.62 to −0.01), which did not withstand adjustment for multiple testing (adjusted p-threshold=0.004). For activity levels and RTV significant differences were not found although the active group usually had better scores than the placebo group (activity: $F_{1,28}=1.44$, $p=0.24$, Est = −0.22, 95% CI −0.61 to 0.16; RTV: $F_{1,28}=1.45$, $p=0.24$, Est = −10.13, 95% CI −27.37 to 7.11). These improvements were greater in the per-protocol analysis which showed, in the active group, a nominally significant reduction in commission errors ($F_{1,23}=5.20$, $p=0.03$, Est = −0.94, 95% CI −1.79 to −0.09), which did not withstand adjustment for multiple testing (adjusted p-threshold=0.004) and a reduction at trend level in RTV ($F_{1,23}=3.69$, $p=0.07$, Est = −16.23, 95% CI −33.71 to 1.25). No significant differences in activity levels were found although the active group usually had better scores than the placebo group ($F_{1,23}=2.26$, $p=0.15$, Est = −0.29; 95% CI −0.70 to 0.11). For the secondary cognitive endpoints, the SART, there were no significant improvements in any of the performance measures in either the active or placebo group. This was also reflected in the per-protocol analysis.

For the symptom domains, there was a nominally significant reduction in hyperactivity/impulsivity scores ($F_{1,28}=5.24$, $p=0.03$, Est = −2.45, 95% CI −4.65 to −0.26) in the active group, which did not withstand adjustment for multiple testing (adjusted p-threshold=0.004). Trends towards improvement in the active group were also seen for inattention ($F_{1,28}=2.83$, $p=0.10$, Est = −2.41, 95% CI −5.34 to 0.52) and emotional lability (CNS-LS: $F_{1,28}=2.74$, $p=0.11$, Est = −3.77, 95% CI −8.44 to 0.89; ALS: $F_{1,28}=1.76$, $p=0.19$, Est = −2.92, 95% CI −7.41 to 1.58). Significant effects were not found for emotional dysregulation measured using the investigator rated WRAADS. Improvements were greater in the per-protocol analysis, which found nominally significant improvements in the active group for hyperactivity/impulsivity scores ($F_{1,23}=5.97$, $p=0.02$, Est −2.83, 95% CI −5.23 to 0.44) (although this did not withstand adjustment for multiple testing (adjusted p-threshold=0.004)); and a trend towards improvement for inattention ($F_{1,23}=3.09$, $p=0.09$, Est −2.72, 95% CI −5.93 to 0.48). For emotional lability using the CNS-LS, no significant differences were found although scores for the active group were generally better than the placebo group ($F_{1,23}=2.52$, $p=0.13$, Est = −3.57, 95% CI −8.24 to 1.09). No significant differences were found for emotional lability or dysregulation measured using the ALS or the WRAADS. There was no change in functional impairment, which was also found in the per-protocol analysis.

Sensitivity analyses are shown in Tables S5-S7. Imputation under the MAR and MNAR assumption yielded similar outcomes. After data imputation there was no longer any indication of a treatment effect on the primary QbTest measure (p=0.6-1.0), activity (p=0.6-1.0) or on QbTest commission errors (p=0.5-0.8). The findings for clinical symptoms remained similar.

3.1. Dosing

For the active medication, in most cases participants titrated to 4-8 sprays (mean number of active sprays used=4.7 (range=1-13, SD=3.3)). In a few cases patients took two sprays at the same time and reported minor adverse experiences. The medication effects were reported as lasting around 3-4 h in most cases. Dosing for the placebo medication was higher than that of the active ($t=2.46$, $p=0.02$, mean number of placebo sprays used=8.5 (range=2.1-14, SD=3.80)) (Table S2).

3.2. Adverse events

Two serious adverse events occurred during the study. One participant on the active medication reported sudden onset of muscular seizures/spasms and stopped taking the medication. This has not been previously reported with Sativex and may have been an atypical reaction to the medication

Table 3 Intent to treat analysis.

	Pre-treatment (M(SD))			Post-treatment (M(SD))						
	Active	Placebo	N A/P	Active	Placebo	N A/P	Est	SE	95% CI	*p*
Primary endpoint										
QbTest	1.73 (0.66)	1.71 (0.95)	14/14	1.32 (0.53)	1.46 (0.91)	15/11	−0.17	0.12	−0.40 to 0.07	0.16
QbTest: individual endpoints										
Qb Activity	2.66 (0.79)	2.61 (0.87)	14/14	2.13 (1.09)	2.43 (0.87)	15/11	−0.22	0.19	−0.61 to 0.16	0.24
Qb CE (%)	1.90 (2.48)	1.36 (1.35)	14/14	1.30 (1.04)	2.19 (3.20)	15/11	−0.81	0.39	−1.62 to -0.01	**0.05****
Qb OE (%)	22.74 (15.22)	26.34 (21.13)	14/14	17.93 (14.51)	21.00 (17.92)	15/11	−1.32	2.75	−6.96 to 4.32	0.64
Qb RTV (ms)	210.79 (59.02)	198.00 (85.06)	14/14	172.00 (43.40)	172.00 (58.62)	15/11	−10.13	8.42	−27.37 to 7.11	0.24
Secondary endpoints										
ADHD Symptoms										
CW Inattention	27.27 (4.42)	27.33 (6.17)	15/15	17.60 (8.87)	21.92 (7.52)	15/13	−2.41	1.43	−5.34 to 0.52	**0.10***
CW Hyp/Imp	19.40 (4.24)	19.00 (7.44)	15/15	10.20 (5.58)	13.85 (7.46)	15/13	−2.45	1.07	−4.65 to -0.26	**0.03****
CW EL	15.60 (5.53)	19.07 (6.26)	15/15	8.47 (5.45)	12.08 (5.75)	15/13	−0.16	1.17	−2.56 to 2.24	0.89
Cognition										
SART CE	36.53 (16.24)	32.71 (16.55)	15/14	28.93 (17.41)	23.00 (15.55)	15/10	−1.23	2.19	−5.73 to 3.27	0.58
SART OE	51.80 (53.67)	41.00 (53.10)	15/14	43.07 (51.95)	20.20 (28.56)	15/10	2.11	5.99	−10.18 to 14.40	0.73
SART RTV	186.85 (51.56)	156.32 (59.88)	15/14	177.04 (58.41)	134.60 (48.64)	15/10	−1.09	7.88	−17.25 to 15.06	0.89
Emotional lability										
CNS-LS	30.67 (15.43)	30.20 (16.95)	15/15	20.13 (15.46)	27.92 (12.44)	15/13	−3.77	2.28	−8.44 to 0.89	0.11
ALS	22.33 (11.14)	22.20 (9.51)	15/15	15.40 (9.49)	21.38 (9.14)	15/13	−2.92	2.19	−7.41 to 1.58	0.19
Functional impairment										
WFIRS Total	1.17 (0.52)	1.11 (0.33)	15/15	0.83 (0.49)	0.77 (0.26)	15/11	−0.02	0.09	−0.20 to 0.15	0.81

Note. A lower score indicates an improved outcome for all measures, M=mean, SD=standard deviation, SE=standard error, Est=estimate, OE=omission errors, CE=commission errors, RTV=reaction time variability.

*$p \leq 0.10$ trend.

**$p \leq 0.05$ (nominally significant).

or an anxiety attack. The second participant was taking the placebo medication and experienced an increased heart rate, tightness of chest and breathing. This required hospital investigation with no cause identified. Mild adverse events were experienced by 3 participants in the active group. 2 reported feeling light-headed, including 1 participant who took 2 sprays at once in the first week of the trial. The other participant in the fourth week of the trial stopped the medication for 6 days for personal reasons and then experienced adverse symptoms after taking 2 sprays within a few hours. In both participants the adverse symptoms resolved after a few hours and they continued with the trial. The third participant reported diarrhoea and stopped taking the medication for 4 days. On resuming medication there were no further complications. Table S8 shows a comparison of minor side effects reported by the active and placebo group on day 28.

4. Discussion

We conducted a pilot randomised placebo controlled experimental trial of Sativex, a cannabinoid medication, in 30 adults with ADHD. We investigated effects on cognitive performance, activity level and behavioural symptoms of ADHD and emotional lability. In the ITT analysis, the primary endpoint, cognitive performance measured by the QbTest showed no statistically significant difference although the overall pattern of findings indicated an improvement (and no worsening of performance) in the active group. For ADHD symptoms, in the active group, nominally significant improvements were found for hyperactivity/impulsivity and trends towards improvements were found for inattention and emotional lability. Although results did not meet significance following adjustment for multiple testing, there were no negative effects on any outcome measure. The per-protocol analysis supported the ITT analysis with greater improvements in the active group for several measures.

With regard to effect size, the point-estimates (the estimated change in slope in the active compared to placebo group) for cognitive performance and ADHD symptoms are similar to those previously reported after treatment of ADHD with stimulant medications (Bijlenga et al., 2015; Michelson et al., 2003; Wehmeier et al., 2012; Weisler et al., 2006). Weisler et al. (2006) in a placebo controlled RCT of stimulant medication in adults with ADHD, found, using the CAARS, an estimated reduction of ∼3–4 in the active compared with placebo group in symptoms of inattention and hyperactivity/impulsivity. This is similar to the estimated reduction of ∼2–3 in the active Sativex group compared with placebo. Bijlenga et al. (2015) found a reduction of 0.6 in the total QbTest score of adults with ADHD after 4 weeks treatment with stimulant medication. This is similar to the reduction of 0.4–0.5 from baseline to follow-up found in the active Sativex group, although comparisons here are limited as this paper did not include a placebo group. Therefore improvements found following treatment with Sativex, although only nominally or non-significant, support the need for further research in this area.

Although no statistically significant improvement was found for the primary endpoint, the overall pattern of results showed an improvement in QbTest performance in the active over the placebo group. This improvement may have been driven by a nominally significant reduction in commission errors, measuring the ability to inhibit a pre-potent response. Moderate reductions, which did not reach statistical significance, were also observed for activity level and RTV. However, these findings were not supported by cognitive performance on the SART and did not withstand sensitivity analyses for data imputation under the MAR and MNAR assumption. It is therefore unclear whether this reflects a small to moderate effect that might be significant in a larger study.

On the other hand, the absence of any negative effect on cognitive performance is of potential interest. The finding that Sativex has no negative effect on cognitive performance in ADHD is surprising, given that cannabis use is generally associated with impaired cognitive function (Crean et al., 2011; Solowij and Battisti, 2008). This is especially so because participants took a dose of medication before completing the QbTest. Acute doses of Δ9-THC have been linked to cannabis-induced cognitive performance deficits including response inhibition (McDonald et al., 2003; Ramaekers et al., 2009), commission and omission errors and mean reaction time (McDonald et al., 2003; Ramaekers et al., 2009), although there is some evidence to the contrary (McDonald et al., 2003). One explanation for this could be related to the equal concentration of CBD relative to Δ9-THC in Sativex, as well as the relatively low dose. Studies in humans have suggested Δ9-THC to be responsible for the cognitive deficits induced by cannabis and that CBD may protect against these impairments (Englund et al., 2012; Morgan et al., 2012, 2010). Given that regular, long-term cannabis use has been associated with cognitive impairment (Lisdahl et al., 2014), it is also possible that the absence of negative effects on cognitive performance could be due to the short length of the study. A future trial would require a longer follow-up period to test this.

For the behavioral symptoms of ADHD, a nominally significant improvement in hyperactivity/impulsivity and a trend towards improvement in inattention were found. Although these did not withstand adjustment for multiple testing, these findings are consistent with the anecdotal reports of ADHD patients. Self-ratings of emotional lability showed a similar trend towards improvement. Although there were no effects on emotional dysregulation measured with the WRAADS, this might have occurred because the active group had lower WRAADS scores at baseline than the placebo group. There was no change in functional impairment, although the study period may have been too short to adequately assess functional outcomes.

One possible explanation for improvements in hyperactivity/impulsivity or inattention may be the anxiolytic effect of CBD and Δ9-THC, which is found after acute administration in healthy subjects (Zuardi et al., 2006). The general calming effects of cannabis could have led to reductions in feelings of restlessness and impulsive behaviour in adults with ADHD, potentially leading to reductions in ADHD symptoms. However, it is notable that these potential effects on ADHD symptoms occurred at a level when there were no marked ‘other’ effects on the mental state. It is therefore feasible that Sativex specifically

targets neural mechanisms that underpin hyperactivity/impulsivity and inattention in ADHD.

One potential mechanism for such an effect is via alterations in striatal dopamine, thought to underlie treatment effects of stimulants (del Campo et al., 2012). Striatal dopamine is thought to modulate the endocannabinoid system (Centonze et al., 2009) and studies have found Δ9-THC administration to increase dopamine in the striatum (Bossong et al., 2015), and other brain regions implicated in ADHD (Stokes et al., 2010). However, not all studies provide data that is consistent with dopamine agonist effects of cannabis (Bloomfield et al., 2014).

The finding of a lack of adverse effects and a trend towards benefit of Sativex on cognitive performance and ADHD symptoms lend some support to the theory that individuals with ADHD use cannabis as a form of self-medication (Mitchell et al., 2016). In this study, subjective accounts from patients in the active group, reported during the blinded phase of the study, are shown in Table S9. Positive feedback from participants was more than double the negative feedback, and most commonly included reports of feeling calmer and improved focus/concentration. Negative feedback was uncommon and included sedative effects (in 3 cases) and slowing of thoughts (in 3 cases).

If replicated in a larger sample, these initial results might reflect individual differences in cannabinoid-response (Englund et al., 2012; Green et al., 2003). Participants with ADHD could represent a subgroup of people who do not experience negative effects from cannabis (D'Souza et al., 2008). Interestingly, heavy cannabis users have been found to show less cognitive impairment following cannabis use than occasional users (Crane et al., 2013; D'Souza et al., 2008; Ramaekers et al., 2009). This could suggest that those who are drawn to cannabis may not experience some of the adverse effects of the drug (D'Souza et al., 2008). Although another possibility is that heavy users develop tolerance to the drug, this explanation is unlikely for the current trial which may have been too short for the development of tolerance (Serpell et al., 2013) and included in the active group only 20% of current cannabis users.

The research of cannabinoids in the treatment of ADHD is undoubtedly controversial, but of considerable interest to clinicians working with adults with ADHD. Many clinicians are aware that ADHD patients tend to report potential benefits of cannabis, and a small number of clinicians in the US have gone as far as prescribing or recommending cannabis for ADHD (Marijuana and Medicine, U.S. House of Representatives, 2004). Furthermore, the medicinal use of cannabinoids is gaining increasing attention. Cannabidiol (CBD) is currently being investigated as a treatment for schizophrenia, anxiety and epilepsy (Devinsky et al., 2014). The more harmful effects of cannabis, such as the association with psychosis and cognitive impairments, have been linked to Δ9-THC, with CBD thought to have more protective effects (Di Forti et al., 2015; Englund et al., 2012). Sativex contains Δ9-THC and CBD in a 1:1 ratio, whereas the UK black market is currently dominated by high Δ9-THC Sinsemilla, with low Δ9-THC cannabis resin increasingly difficult to obtain (Potter et al., 2008). Pharmaceutical formulations of cannabinoids could therefore potentially provide safe alternatives to the use of street cannabis by some individuals with ADHD.

There are several limitations to this study. In particular, we were underpowered to detect significant effects and provide accurate estimates of effect size. This means that we cannot rule out the possibility that the observed lack of negative effects on Qb Test performance could reflect a type II error. Furthermore, cognitive performance and not ADHD symptoms were the primary outcome. For our primary endpoint we observed a small Cohen's d of 0.2, equating to ~8% power to detect a statistically significant result, whereas we had larger effects in secondary clinical outcomes. Low power was however unavoidable given this was an initial pilot study, which aimed to assess feasibility and potential effect sizes in order to inform the design of a larger trial, recommended as a required stage in the evaluation of a new treatment (Craig et al., 2008). Our results have provided evidence that supports the need for a larger trial. Given the largest treatment effects were found for the secondary outcome hyperactivity/impulsivity, we would consider using this as our primary endpoint in a future trial. Such a trial would need approximately 84 participants distributed in a 1:1 ratio between the treatment arms to achieve 80% power (d=0.6, α=0.05).

Although the trial was double blind, correct guess-rates for active/placebo status were high (93% active and 85% placebo). Lack of blinding may be associated with exaggerated estimates of intervention effects (Wood et al., 2008) and could potentially explain the larger effects seen for symptoms, which are based on subjective reports and therefore prone to bias (Wood et al., 2008). Potential exaggeration of treatment effects must be taken into account when interpreting our results. One potential solution to this problem is for a future trial of Sativex to compare against an active medication such as methylphenidate. There was a greater drop-out rate in the placebo compared to the active group which might reflect patient's views of a relative benefit to the active medication. Despite sensitivity analysis indicating the MAR assumption could be accepted, increased placebo group drop-out is indicative of non-random drop-out due to lack of a treatment effect. Multiple imputation in the sensitivity analysis gave an overall negative effect for the QbTest, indicating that increased drop-out in the placebo compared to the active group may have inflated effect sizes for the QbTest; and effects on symptoms were also reduced.

The titration schedule aimed to reach an optimal dose based on patient reports of the control of their ADHD symptoms. As we were not aware of other studies of Sativex in ADHD, we had no prior guidance on optimal dosing in ADHD and based the initial titration protocol on that recommended by GW Pharma. However it quickly became clear that the titration schedule was too high and that lower doses seemed to be effective. Although we advised participants to remain at a lower dose once they found a beneficial effect, at follow-up a small number of participants on the active medication had taken a high dose for the majority of the trial and verbally reported that they did not derive benefits. Participants in the placebo group also took a significantly higher number of sprays a day than those in the active group, which might have introduced a bias due to a perceived 'dosing' effect. However, due to the failure of the blind, this is unlikely.

Although the above observations during the study give some indication of optimal dosing of Sativex in ADHD, the

study was not designed as a dose finding study, and no recommendation on dose can be made. In the current study it may have been difficult to separate spontaneous improvement over time with response to higher doses or cumulative drug exposure, and non-responders may have been titrated to higher doses. Therefore dosing recommendations from this study cannot be accurately made as they may reflect the highest tolerable dose. Such doses may be in excess of what is really necessary and could result in increased undesirable side-effects (ICH Expert Working Group, 1994). Although, feedback during the study and average doses (Table S2) indicate a maximum dose of 8 sprays per day, with an optimal dose of around 3–5 sprays per day, a dose-response study needs to be conducted prior to a larger trial in order to determine the lowest effective (and best tolerated) dose of Sativex in ADHD (ICH Expert Working Group, 1994; Sacks et al., 2014).

The potential for abuse of Sativex and the development of tolerance should be considered. The potential for abuse of Sativex was previously examined in a treatment trial with recreational cannabis users (Schoedel et al., 2011). At a low dose (4 sprays) no more potential for abuse than the placebo medication was found, however higher doses (8-16 sprays) showed more potential for abuse than placebo. Sativex may therefore carry risks of abuse in adult patients with ADHD. It is important to note, however, that stimulant medication which is currently prescribed for ADHD is also a controlled drug with potential for abuse when used inappropriately. Tolerance has been investigated previously in a study of the long-term use of Sativex. No evidence of tolerance/dependence was seen in patients with multiple sclerosis, who took Sativex spray for between 1 and 3 years, indicated by the maintenance of a relatively stable dose of Sativex over a period of a year (Serpell et al., 2013).

The occurrence of only one serious AE in the active group suggests that, as a whole, the medication was well tolerated. The adverse effect rating scale showed no significant difference in side effects between the placebo and active groups. Three participants in the active group experienced a mild adverse event, which are listed as common AEs of Sativex.

In conclusion, this experimental pilot study provides an initial evaluation of the potential effects of Sativex on cognitive impairment and behavioural symptoms in adults with ADHD. Results did not meet significance following correction for multiple testing so are inconclusive. QbTest performance (the primary outcome incorporating cognitive performance and activity level) was not impaired following cannabinoid use. Although this finding could reflect a type II error, the overall pattern of findings did not indicate adverse effects on cognitive performance in the ADHD sample studied. Nominally significant improvements were also seen in the hyperactive-impulsive symptom domain, with an overall pattern of improvement in the other symptom domains of ADHD. While not definitive, these findings are consistent with the self-medication hypothesis of cannabis use in ADHD, and support further investigations of the endocannabinoid system as a potential treatment target for ADHD. Based on these findings, we suggest a dose-response study is needed prior to any further investigations of Sativex in ADHD; followed by a more conclusive study, which would require a sample of around 100 participants or more, and a longer follow-up period of 3–6 months. The findings also provide preliminary support for further investigations of other compounds targeting the endocannabinoid system in ADHD.

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Contributors

The study was developed by PA and REC. The trial was coordinated and data collected by EW, PA and REC. The statistical analysis was carried out by SS and REC. The first draft of the report was written by REC under the guidance of all authors. All authors assisted in the interpretation of the data, critically revised the report and contributed important intellectual content.

Conflict of interest

At the time this work was undertaken, Ruth Cooper was a Ph.D. student at King's College London (KCL) funded by a research grant to Philip Asherson from Vifor Pharma. Philip Asherson received funds for consultancy or sponsored talks on behalf of KCL for Shire, Lilly, Novartis, Janssen and PCM Scientific. He received research or education funds on behalf of KCL from Shire, Lilly, Novartis, Janssen, Vifor Pharma and QB Tech. The Sativex medication was provided free of charge to Philip Asherson from GW Pharma. Emma Williams, Seth Seegobin, Charlotte Tye and Jonna Kuntsi declare no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2017.05.005.

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