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Cannabinoid Augmentation of Exposure-Based Psychotherapy for Obsessive-Compulsive Disorder

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TO THE EDITORS:

Obsessive-compulsive disorder (OCD) is a disabling illness characterized by recurrent intrusive thoughts and repetitive behaviors that cause significant functional impairment (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition)*. First-line treatments include serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy (CBT) with exposure and response prevention (EX/RP). However, more than one third of patients do not respond to either, and less than half achieve remission (i.e. minimal symptoms following treatment).[1] New treatment approaches are needed.

The endocannabinoid system (ECS) is a regulatory neurotransmitter system that is ubiquitous throughout the central nervous system.[2] Emerging preclinical and clinical data linking the ECS to OCD-relevant neurocognitive processes including anxiety, fear, and repetitive behaviors[3] have sparked interest in this system as a possible target for novel OCD treatments. For example, a series of rodent studies implicated the cannabinoid 1 receptor (CB1R, the primary receptor for the ECS in the brain) in maintaining an appropriate balance between goal-directed and habitual behaviors,[4] while both preclinical models and human studies have found that CB1R agonists can attenuate the response to threatening stimuli and facilitate extinction of conditioned fear.[5] OCD has been associated with an overreliance on habit,[6] excessive responsiveness to threat,[7] and deficient fear extinction.[8]

Taken together, these findings suggest that agents targeting elements of the ECS (cannabinoids) could modulate the above neurocognitive processes to improve OCD symptoms. For instance, medication targeting CB1R might influence the balance between

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goal-directed and habitual activity to reduce compulsive behaviors. Alternatively, given their capacity to enhance fear extinction, cannabinoids could potentially be used to augment EX/RP, which is thought to reduce OCD symptoms in part by facilitating extinction learning.[9] Though EX/RP is a highly effective treatment for OCD, up to half of patients who receive it will remain symptomatic, and some will not improve at all.[10] Both D-cycloserine[11] and ketamine[12] have been tested as possible EX/RP-augmenting agents. However, despite these potential applications, to date no studies have tested the effects of a cannabinoid on OCD symptoms, either as monotherapy or combined with EX/RP.

Here, we describe a pilot trial of nabilone, a synthetic form of THC and CB1R agonist. The goal was to assess the acceptability, tolerability, and preliminary efficacy of nabilone, alone and combined with EX/RP, in adults with OCD. The study was conducted at the New York State Psychiatric Institute from February 2017 to January 2019 and was registered at ClinicalTrials.gov (identifier: NCT02911324). With institutional review board approval, we recruited 11 unmedicated outpatients (ages 18-60) who met DSM-5 criteria for OCD with at least moderate symptoms (Yale-Brown Obsessive Compulsive Scale [YBOCS] score ≥16).[13] Exclusion criteria included a history of bipolar disorder or psychosis, severe depression (Hamilton Depression Rating Scale, 17-item [HDRS-17][14] score > 25), current EX/RP, prior adverse response to cannabis or a cannabinoid, positive urine toxicology screen or substance use disorder, pregnancy or nursing, or other medical/psychiatric conditions preventing safe participation. All participants provided written informed consent before enrolling.

Eligible participants were randomly assigned to receive 1) nabilone only, or 2) nabilone +EX/RP using a block randomization procedure that balanced the two conditions for every 6 entrants into the study. Both groups were treated for 4 weeks, after which treatment was stopped and participants were offered referrals at their request. At weeks 0, 2, and 4, independent evaluators blind to the study design rated OCD symptoms using the YBOCS (the primary outcome measure) and depression symptoms using the HDRS-17. At each time point, patients also self-reported anxiety and stress using the Depression Anxiety Stress scale (DASS),[15] and in the EX/RP group, study therapists evaluated adherence using the Patient EX/RP rating scale (PEAS).[16] All participants met weekly with a study physician who assessed blood pressure (BP), heart rate (HR), weight, medication side effects (via a 28-item self-report scale assessing the most commonly-reported side effects from the nabilone package insert), and medication adherence (by verbal report). One month after completing the protocol and stopping all study treatments (week 8), participants completed an additional follow-up assessment including all of the above measures.

All participants were prescribed 1 mg BID nabilone (Cesamet™, Mylan Pharmaceuticals, Canonsburg, PA) taken orally for 28 days. As dose-ranging studies have not been conducted for nabilone in OCD populations, a 1mg BID dose was chosen given prior studies demonstrating tolerability of a 3mg BID dose among marijuana smokers (who would be expected to have a higher THC tolerance than participants in this study).[17] Participants in the EX/RP group were treated using a standard protocol as outlined in Foa et al.[18] As in other pharmacological augmentation studies of EX/RP,[11, 19] the course was abbreviated from the standard of 17 sessions over eight weeks. Instead, participants received nine 90-minute sessions over four weeks, including one treatment planning session, eight exposure

sessions, and between-session phone check-ins. Participants completed *in vivo* and imaginal exposures during which they confronted feared stimuli without ritualizing. As homework, they were asked to record rituals and conduct daily self-guided exposures.

Of the 35 potential participants screened, 10 did not meet inclusion/exclusion criteria. Eleven were eligible but chose not to participate due to time commitment (n=9) or were lost to follow-up during a nationwide shortage of nabilone lasting several months (n=2). Fifteen participants were randomized; three withdrew (nabilone only, n=1; nabilone+EX/RP, n=2) after a single dose of study medication due to increased anxiety lasting 12-24 hours. Following these withdrawals, we modified the dosing schedule such that future participants were started at a dose of 0.25 to 0.5mg BID and gradually uptitrated to 1mg BID during the first 1.5 weeks of the study. Using this dosing strategy, no further participants withdrew. One additional participant was removed by the study team due to gross inconsistencies between the participant's verbal reports and written self-report forms.

Eleven participants completed the protocol (nabilone only, n=6; nabilone+EX/RP, n=5). Demographic/clinical characteristics and YBOCS scores for both randomization groups are presented in Table 1. On average, patients had severe OCD symptoms. Baseline depression symptoms were low; two participants (18%) met criteria for comorbid major depression (HDRS-17 scores of 12 and 14). All participants reported adherence to medication. PEAS scores showed adherence to EXRP (mean=5.84, SD=0.65). No serious adverse events occurred during the study. The most commonly-reported side effects at week 1 were dry mouth (n=9), nervousness (n=8), drowsiness (n=7), difficulty concentrating (n=4), disorientation (n=4), and forgetfulness (n=4). By week 4, the most commonly-reported side effects were dry mouth (n=5), forgetfulness (n=5), disorientation (n=4), and difficulty concentrating (n=3). The vast majority of side effects at week 4 were rated as "mild", with no subject rating any side effect greater than "moderate".

Adjusting for baseline YBOCS scores, one-way ANCOVA revealed a significant effect of treatment group on YBOCS change score ($F[1, 8]=16.81$, $p=.005$) with the nabilone+EX/RP group showing significantly greater change than nabilone alone (mean [SE]=11.3 [1.6] vs. mean [SE]=2.7 [1.4], respectively). There were no significant differences in either HDRS-17 or DASS scores between week 0 and week 4 (all p-values>.1). At one-month follow-up (week 8), one participant in the nabilone only group had started an SSRI; none had received psychotherapy. All participants in the nabilone+EX/RP group remained unmedicated and did not receive additional psychotherapy at this assessment. At week 8, mean YBOCS for the nabilone only group was 24.2 (SD=5.5) and for the nabilone+EX/RP group was 15.8 (SD=4.6). Thus, compared to week 4, week 8 YBOCS changed by less than 2 points for both groups.

Over the same time period of this study, 21 other patients meeting identical inclusion/exclusion criteria participated in a separate trial in which they received EX/RP alone (17 90-minute sessions over 8 weeks) from the same therapists. These participants were not randomized into the present study and thus cannot be compared statistically with our sample. Their data are presented as a rough benchmark to estimate the effects of EX/RP alone. Baseline YBOCS severity was comparable between this non-randomized sample and

both randomized groups, but the 4-week change in YBOCS was less than in the nabilone +EX/RP group.

DISCUSSION

This small randomized pilot trial of nabilone, alone or combined with EX/RP over 4 weeks, in adults with OCD is the first to examine the effects of a cannabinoid in OCD. There are three key findings. First, nabilone appeared to be acceptable to individuals with OCD, as evidenced by our success in recruiting participants into the study. Of note, the majority of participants were either entirely naïve to cannabis/cannabinoids or had minimal prior experience (less than 5 lifetime occasions), indicating that nabilone's acceptability is not limited to prior cannabis users.

Second, nabilone was generally well-tolerated. There were no severe adverse events, and side effects including anxiety and dry mouth were generally mild and improved with time. Three participants withdrew after a single dose of nabilone due to increased anxiety. Decreasing the initial dose to 0.5mg or even 0.25mg BID followed by gradual up-titration appeared to reduce initial anxiety effects and improve tolerability such that no further participants withdrew. This finding mirrors preclinical data which show that adding low initial doses can mitigate the aversiveness of THC and its analogues.[21] Notably, no participants reported euphoria, which may alleviate concerns about nabilone's abuse potential.

Third, nabilone produced little change in OCD symptoms on its own, but yielded a large mean change in YBOCS scores when combined with an abbreviated EX/RP protocol. The degree of change for nabilone+EX/RP was nearly twice that observed in the non-randomized benchmark sample (who received EX/RP alone from the same therapists), and the observed improvement in YBOCS appeared to be maintained one month after completing the study protocol.

EX/RP has been described as "fear extinction used therapeutically",[9] and as described above, studies in both animal models and humans show that cannabinoids can facilitate extinction learning. Our findings are consistent with this hypothesized mechanism. However, this preliminary, observational study of nabilone's acceptability and tolerability in patients with OCD included a small sample size and did not randomize patients to receive pill placebo or EX/RP alone. A larger controlled trial is necessary before any definitive conclusions can be drawn about nabilone's efficacy as monotherapy or to augment EX/RP. Moreover, this study was not designed to enable confirmation of nabilone's mechanism. Thus, additional study is needed to confirm nabilone's target in the brain (for example, by using task-based fMRI to show that nabilone alters function in fear circuitry in patients with OCD).

Despite the above limitations, this study serves as an important first step towards determining whether nabilone and other cannabinoids may have a therapeutic role in OCD. Though preliminary, our results provide the first clinical hints suggesting that nabilone could be used to augment EX/RP for individuals with OCD. Moreover, we found that nabilone is

acceptable and tolerable in this population, indicating that a randomized, placebo-controlled trial in an expanded sample would be feasible to conduct. Replication of our findings in such a trial would support nabilone's utility to augment exposure-based treatments for OCD and could point towards the ECS as a novel target for treating this debilitating condition.

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Table 1

Results

Demographic and Clinical Characteristics[a]		
Variable	**Nabilone only (n=6)**	**Nabilone+EX/RP (n=5)**
Age, mean (SD); range, y	35.5 (14.6), 22-60	30.8 (10.4); 23-49
Male	3 (50)	4 (80)
Single	6 (100)	5 (100)
Hispanic	0 (0)	1 (20)
Race		
White	3 (50)	3 (60)
Black	1 (17)	0 (0)
Asian	2 (33)	1 (20)
other	0 (0)	1 (20)
Baseline YBOCS score, mean (SD)	26.5 (4.2)	25.4 (4.8)
Baseline HDRS-17 score, mean (SD)	6.5 (5.3)	5.0 (1.0)

Mean YBOCS Scores[a]			
Assessment	**Nabilone only (n=6)**	**Nabilone+EX/RP (n=5)**	**EX/RP only (Non-randomized Benchmark Group, n=21)**
Week 0	26.5 (4.2)	25.4 (4.8)	25.1 (3.6)
Week 4	24.0 (6.9)	14.2 (4.8)	19.1 (6.8)
Change Score[b]	2.5 (3.6)	11.2 (3.4)	6.1 (5.2)

[a] Values shown as mean (SD)

[b] Change Score = (week 4 YBOCS – week 0 YBOCS)

Abbreviations: YBOCS = Yale-Brown Obsessive-Compulsive Scale; HDRS-17 = 17-item Hamilton Depression Rating Scale