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Behavioral Effects of Pregabalin and Cannabis
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Study Protocol

Adult men and women, aged 18-50, who could speak and read English were recruited from the local community using flyers, social media, research participant registries, outreach activities, paid digital and print advertisements and referrals. Potential participants were required to report daily or near-daily cannabis use (i.e., at least 25 days per month of use as defined in Budney et al., 2007) and provide a urine sample positive for cannabis use and negative for other recent illicit substance use. Individuals with a history of serious physical disease or non-personality psychiatric disorders according to DSM-IV (computerized Structured Clinical Interview for DSM-IV, Psychmanager, Multi-Health Systems Inc., North Tonawanda, NY; 300 mg/day pregabalin group) or DSM-5 (online SAGE-SR, Telesage Inc., Chapel Hill, NC; 450 mg/day pregabalin group) criteria, other than disordered use (i.e., abuse and/or dependence for DSM-IV and use disorder for DSM-5) of nicotine and/or cannabis, were excluded from participating. Further exclusion criteria included seeking or currently receiving treatment for drug use, desire to reduce drug use or abstain from use independent of the study procedures, medical screening outcomes outside normal ranges deemed clinically significant by the study physician, history of, or current, angioedema, seizure disorder, use of prescription medications other than hormonal contraceptives or antibiotics, and pregnancy in women. Participants were also excluded for having first-degree family history of either cardiovascular disease that resulted in premature death or seizure disorder.

This study used a placebo-controlled, double-blind, pregabalin- and cannabis-dose counterbalanced, mixed within- and between-subjects design. Participants were enrolled as outpatients. Two active doses of pregabalin, 300 and 450 mg/day, were tested in separate groups of participants (i.e., active pregabalin dose [300 and 450 mg/day] was a between-subjects factor). In the 300 mg/day group, participants attended two practice sessions prior to completing two 11-day

pregabalin maintenance phases (150 mg administered twice per day for a total daily dose of 300 mg, or placebo). Each maintenance phase began on a Monday and ended on the Thursday of the following week, with a 10-day inter-phase interval. Each phase consisted of seven maintenance-only days (Monday through the following Sunday) and four experimental sessions (Monday through Thursday). During experimental sessions, maintenance continued, and participants completed two 2-day blocks of sampling and self-administration sessions to determine the reinforcing effects of cannabis (0 and 5.9% THC). In this way, cannabis concentration (0 and 5.9%) THC and pregabalin dose (0 and 300 mg/day) were within-subjects factors. In the 450 mg/day group, participants received placebo and 450 mg of pregabalin per day (divided into two daily doses of 225 mg), and the maintenance phase lasted 15 days (Thursday through Thursday), with a 6-day inter-phase interval.

Participants were required to abstain from illicit drugs other than cannabis throughout participation. Daily urine tests to assess recent drug use and pregnancy were negative throughout. Participants were also asked to avoid any over-the-counter medication, with the exception of non-steroidal anti-inflammatory analgesics. On maintenance-only days, participants were administered the first of the two daily pregabalin doses and were given a “take-home” dose. Participants did not report to the laboratory on weekends. On Fridays, participants received additional take-home capsules. At the end of each maintenance phase, participants were tapered off of pregabalin. Practice and experimental (i.e., sampling and self-administration) sessions were conducted on weekdays and lasted 6.5 h. Participants were asked to refrain from food, caffeine, alcohol, tobacco and cannabis use prior to arrival. At intake, a breath sample was obtained to assess recent alcohol use. Participants also completed a field sobriety test (Toland & Green, 1991) and were observed by trained research staff for cannabis intoxication (e.g., bloodshot, glassy eyes). Participants were required to consume a low-fat snack at intake. Participants who smoked tobacco cigarettes were allowed to smoke a single tobacco cigarette upon arrival to the laboratory to avoid testing under conditions of nicotine withdrawal. They were not allowed to smoke again until the session had ended. Participants were reassessed at the end of the session for possible intoxication and/or impairment using the field

sobriety test prior to release. In addition, participants were required to report no drug effects. The first practice session duplicated a sampling session and the second a self-administration session. Participants smoked un-blinded placebo cannabis cigarettes to become acquainted with the paced smoking procedure. On the practice self-administration session, participants were required to work to receive the maximum number of puffs (8) to familiarize them with the response requirements. Sampling Sessions were conducted to familiarize participants with the effects of the cannabis they could work for in a subsequent session. Participants were instructed to pay attention to the effects of the cannabis, as they would be given the opportunity to work to receive puffs from the same cannabis condition in the next session. During self-administration sessions, immediately after maintenance dosing, participants completed a self-administration task to earn puffs of cannabis sampled the day prior and/or an alternative monetary reinforcer ($0.50), which were concurrently available on independent progressive-ratio (PR) schedules. A maximum of 8 reinforcers could be earned (e.g., 8 puffs of cannabis, $4 or some combination of cannabis puffs and money), and participants were required to make a total of 8 choices. The initial response requirement for each reinforcer was 400 responses (i.e., mouse clicks). The completion of a response requirement for a given reinforcer (i.e., cannabis puffs or money) increased the response requirement for that reinforcer by 200. Once the task was complete, participants self-administered the number of puffs earned using the paced smoking procedure. Cannabis cigarettes (0 and 5.9% THC) were provided by the National Institute on Drug Abuse. Pregabalin (0, 150 and 225 mg) was administered in one opaque capsule containing commercially available Lyrica® (Pfizer, Inc., New York, NY) twice per day. Doses were based on those recommended for neuropathic pain and seizures (i.e., 150-600 mg/day). Doses were escalated across the initial maintenance days up to the target dose, based on the Product Information recommendations. Prior to drug administration, heart rate was assessed. If heart rate exceeded 100 bpm, drug administration would have been withheld, but this did not occur.

Data Analyses

To account for the correlation among repeated measures, generalized estimating equations with random participant effect were used to fit a linear model for the primary outcome in both groups. Fixed effects for pregabalin and cannabis, as well as their interaction, were used as predictors. Tests were two-sided and utilized a 5% significance level. Significant interactions were followed with post-hoc pair-wise comparisons. Analyses were conducted in SAS version 9.4.