

# #35: Cannabidiol (CBD) and Tetrahydrocannabinol (THC) Combinations as Adjunctive Therapy in Drug Resistant Epilepsy



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## Background and Rationale:

- Use of cannabis preparations in the treatment of epilepsy and seizures is an ancient practice in medicine, but only recently have wide scale studies thoroughly begun to verify its efficacy and safety<sup>1</sup>. Preclinical models and now three large placebo-controlled, double-blind clinical trials have demonstrated anticonvulsant efficacy of cannabidiol (CBD)<sup>2</sup>. Clinical data for efficacy of tetrahydrocannabinol (THC), on the other hand, remain limited to retrospective surveys<sup>1</sup>. Some have suggested a synergistic effect of THC or other cannabinoids added to CBD therapy regimens (the so-called “entourage effect”) to account for anecdotal reports of THC efficacy at odds with this evidence base<sup>1</sup>.
- Previously published clinical reports regarding efficacy of CBD/THC derive from various state medical marijuana programs that include wide variation in formulations and minimal prescriber involvement<sup>3</sup>. Because the Texas Compassionate Use Program (TCUP) includes a centralized database, requires physician oversight of therapy, regulates THC concentration, and limits production to only three licensed dispensaries, a unique opportunity exists to observe clinical response with consistent CBD:THC formulations<sup>4</sup>.
- Our IRB-approved, unblinded, retrospective cohort study tracked the reported experiences of patients with drug-resistant epilepsy (DRE) of various etiologies<sup>5</sup>. Here, we further examined the effect on seizure control over time for a subset of subjects treated with various combinations of FDA-approved, >99% pure CBD (Epidiolex®) and dispensary-prescribed CBD:THC combinations.

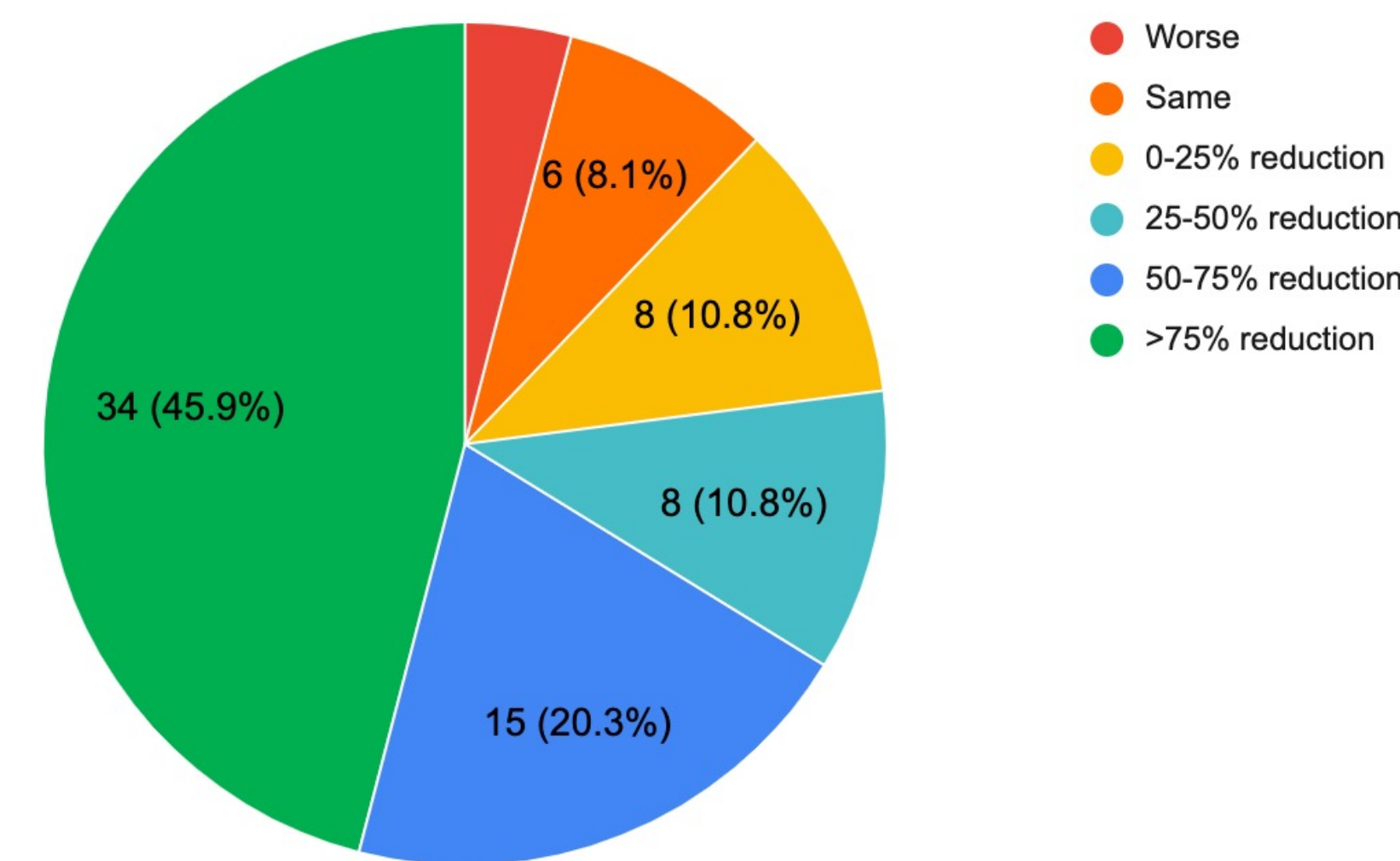
## Methods:

- Between Feb 2018 – Jan 2021, two authors (ALC, KK), enrolled and treated 212 patients with cannabis-derived CBD:THC preparations through the Texas Compassionate Use Program. Though three dispensaries are licensed in Texas, all treatment reported here came from a single dispensary source. Prescribers initiated and adjusted dosage by their clinical judgement without regard to pre-specified endpoints.
- Each clinic visit was reviewed retrospectively. At each visit, the patient/care-giver-reported change in seizure control, counted in quartiles compared to baseline (before CBD treatment), and the corresponding ratio of CBD:THC were recorded. CBD:THC of the prescription with greatest seizure reduction for each patient was noted.

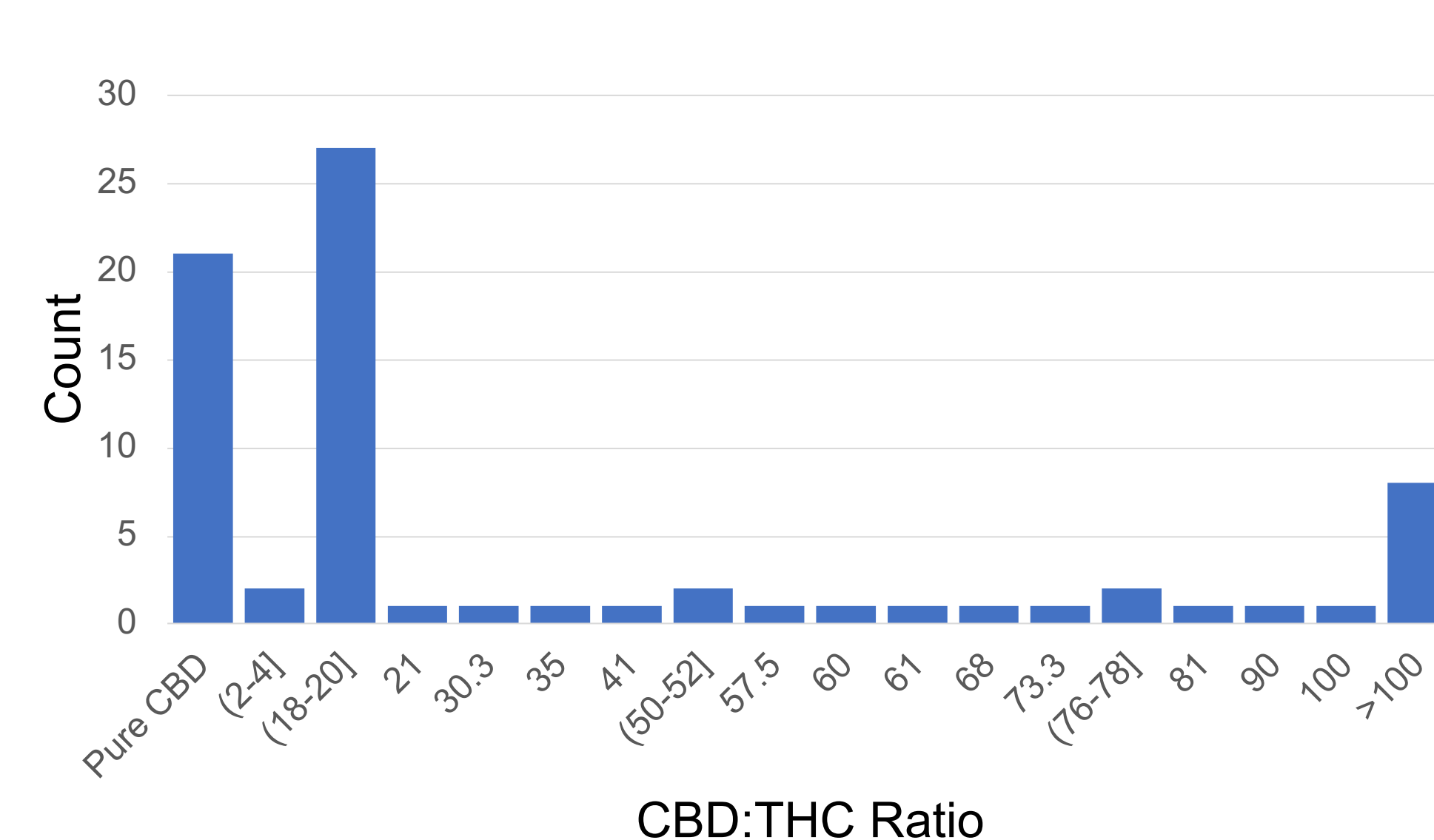
Demographics:	
Age at time of first Rx (months) - Median (range)	152 (24 - 309)
Male sex - no. (%)	41 (55)
Duration on CBD (days) - Median (range)	805 (400 - 1141)
Etiology - no. of patients (%)	
Structural	24 (32)
Genetic	24 (32)
Unkown	26 (35)

## Results:

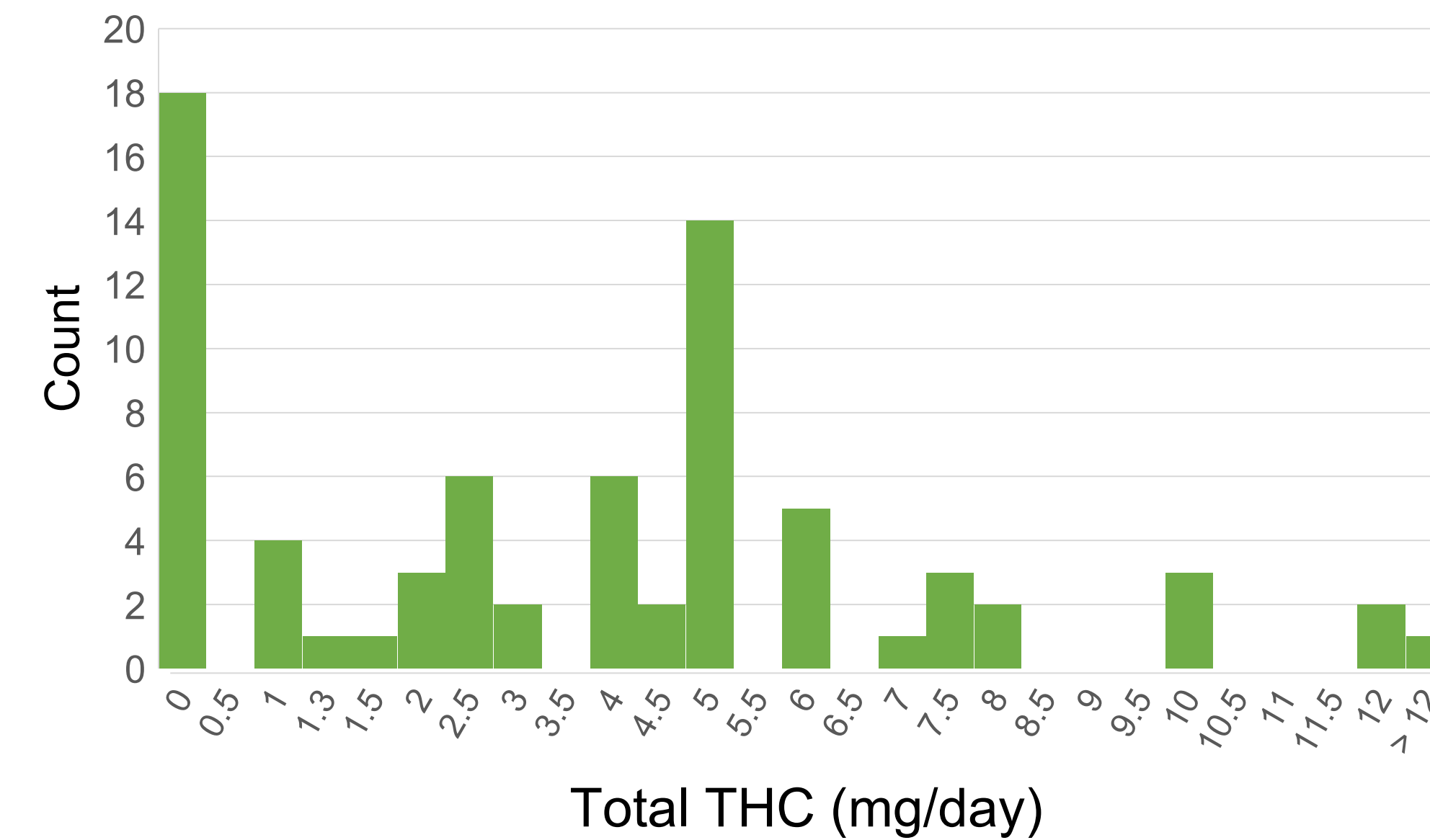
Greatest Seizure Reduction from Baseline



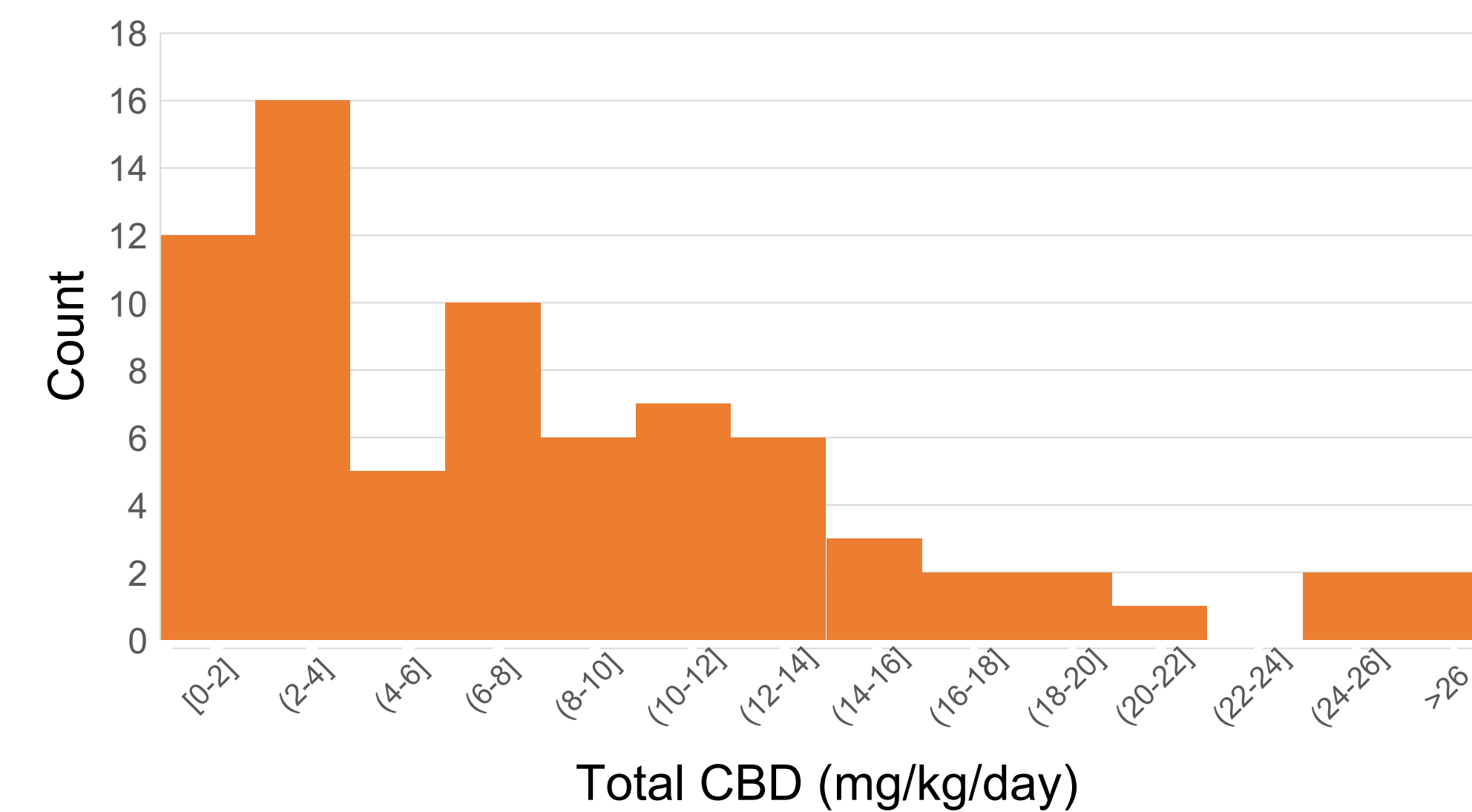
CBD:THC at Greatest Seizure Reduction from Baseline



Total THC at Greatest Seizure Reduction from Baseline



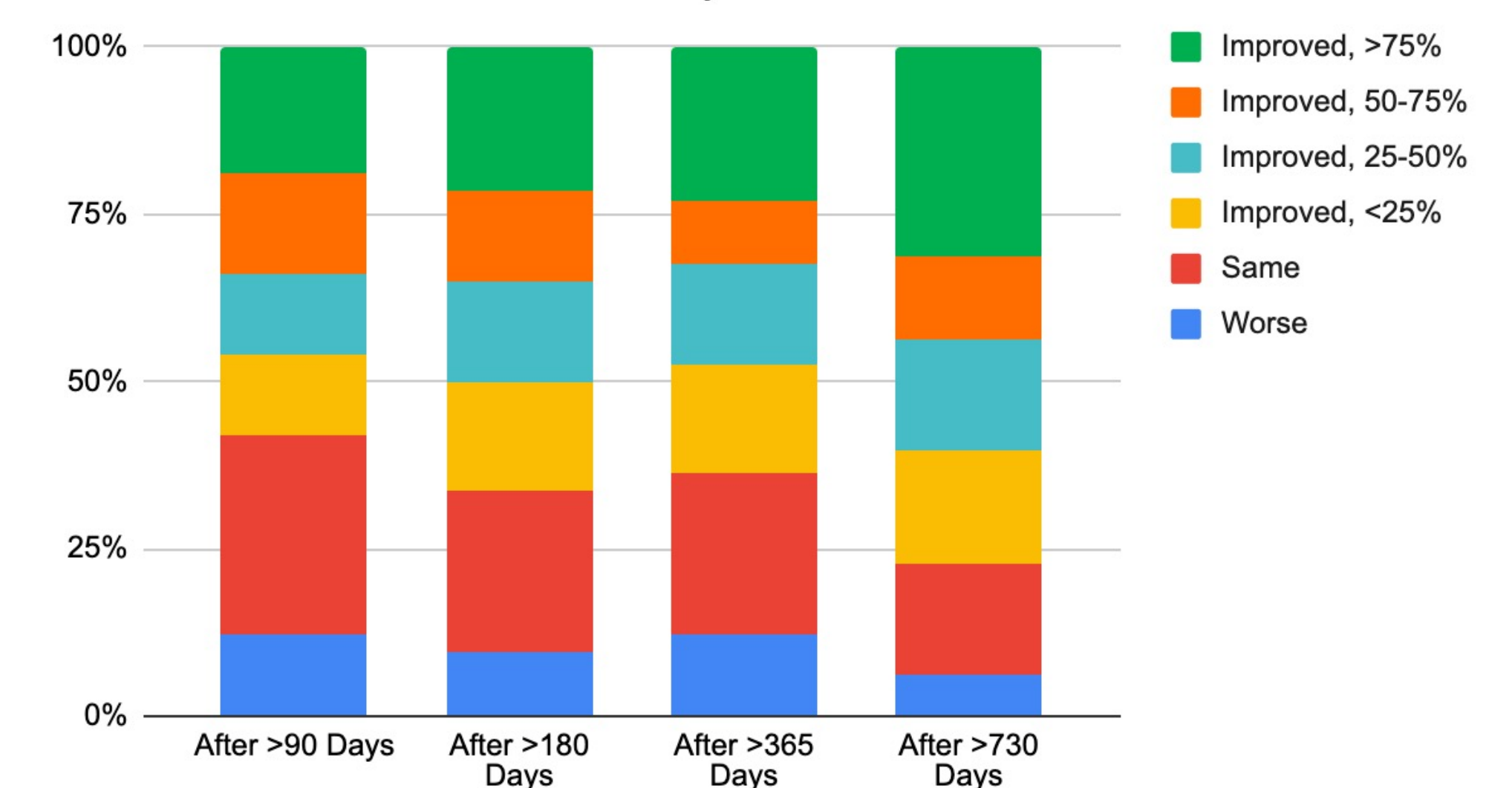
Total CBD at Greatest Seizure Reduction from Baseline



Seizure response at last clinic visit was recorded

Enduring Response	Number of Subjects (%)
Better	57 (77%)
Same	10 (14%)
Worse	7 (9%)

Seizure Response Over Time



## Interpretation and Implications:

- Patients reported greatest seizure reduction at different CBD:THC ratios, however because 20:1 was the first prescription for most patients, many stayed at this ratio.
- As Epidiolex became available, much higher CBD doses and CBD:THC ratios became possible. Conversely, beginning in late 2019, the introduction of balanced formulations with low CBD content but consistent THC concentration allowed for combination therapy to yield lower CBD:THC ratios.
- As potential CBD/THC regimes expanded, provider strategy in prescribing CBD/THC to optimize seizure response changed. In addition, THC is not always added for seizure response, but was also added or retained for other symptoms, or to ameliorate adverse effects (agitation, anorexia, insomnia) of CBD at times.
- Interpretation of causality is further limited by other concurrent treatment changes, including other medication adjustments in most patients and alternative therapies (VNS, diet therapy) in a small minority.
- The size of our cohort, single source of stable combination therapy, and duration of follow-up significantly expand the clinical data for outcomes in CBD/THC therapy for epilepsy. There is further need for prospective study evaluating the potential of CBD/THC combination therapies for seizure control.

## References:

- Yao I, Stein E, Maggio N. 2019, Pharmacology & Therapeutics; 10.1016/j.pharmthera.2019.06.002
- Devinsky O, Patel A, Cross H, et al. 2018 N Engl J Med; 10.1056/NEJMoa1714631
- Porcari G, Fu C, Doll E, et al. 2018, Epilepsy & Behavior; 10.1016/j.yebeh.2018.01.026
- Fortin-Camacho C. 2017, SSRN; 10.2139/ssrn.2893809
- Campbell D, Whitehall R, Keough K, et al. Amer Epil Society. Seattle, WA; 12/07/2020.

212 patients enrolled through Texas Compassionate Use by authors during study period

135 with DRE, treated with CBD:THC preparations consented to review

84 identified as prescribed Epidiolex and dispensary source CBD at some point during therapy

10 excluded on review:

- Insufficient data (4)
- Not on study treatment (CBD:THC or >99% pure CBD) (2)
- Non-dispensary CBD use during study (2)
- Epilepsy surgery during study (2)

74 reviewed for study