Impact of Adverse Effects on Treatment Adherence to Cannabidiol in Patients With Dravet Syndrome: A Systematic Review

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Abstract

Introduction: Dravet Syndrome, a severe, genetic, and refractory epileptic encephalopathy, presents significant therapeutic challenges. While conventional treatments like valproic acid and clobazam have limited efficacy, cannabidiol (CBD) has emerged as a promising adjunctive therapy for seizure control. However, its long-term safety profile, associated adverse events (AEs), and sustained clinical impact require further investigation. This study critically evaluates CBD's effectiveness and safety in Dravet Syndrome treatment.

Method: We conducted a systematic literature review following PRISMA 2020 guidelines, including English-language randomized controlled trials (RCTs) on Dravet Syndrome treated with CBD, valproic acid, or clobazam. Searches spanned major databases including PUBMED/MEDLINE, Web of Science, Scopus, Embase, Cochrane Library, LILACS, and Scielo. We extracted and qualitatively analyzed data on safety, AEs, discontinuation, and clinical benefits. Methodological quality was assessed using the ROB 2 (Risk of Bias 2) tool.

Result: Ten clinical studies (n ≈ 1,276) were included, involving Dravet Syndrome patients treated with CBD (5–20 mg/kg/day) for 14 weeks to 3 years. Significant efficacy was observed, with mean seizure reductions from 38% to 85%. A 10 mg/kg/day CBD dose showed a 48.7% seizure reduction versus 26.9% with placebo, with fewer AEs than 20 mg/kg/day. AEs occurred in 94%–97% of patients, including diarrhea (up to 69%), fever (43%), decreased appetite (31%), and somnolence (28%). Hepatotoxicity (17%–22%) was primarily linked to concomitant valproate use, with 10 mg/kg/day CBD showing lower hepatic risk. Discontinuation rates ranged from 6%–9%, but retention fell to 45% over 3 years. Sedation (due to clobazam interaction) and hepatic toxicity were primary reasons for withdrawal,emphasizing dose adjustment and laboratory monitoring.

Discussion: Our review, compared to other systematic reviews, found convergences in common AEs (somnolence, fatigue) as mild-to-moderate. However, discrepancies in rare AEs and methodologies were apparent, highlighting review heterogeneity. Polypharmacy in Dravet Syndrome complicates identifying specific drug interaction-related AEs. Many RCTs showed methodological fragilities, lacking standardized AE/quality-of-life scales, which undermines confidence in outcomes and may lead to underreporting. This issue is amplified by "scientific hype" and CBD's substantial financial impact, suggesting the need for greater transparency and rigor in future research.

Conclusions:CBD's AEs generally have a limited impact on treatment discontinuation, with common symptoms usually well-tolerated at titrated regimens up to 20 mg/kg/day.

References

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