

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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DOI: 10.1056/NEJMc1805809

## Cannabidiol in the Lennox–Gastaut Syndrome

**To the Editor:** Devinsky et al. (May 17 issue)<sup>1</sup> randomly assigned patients with the Lennox–Gastaut syndrome to one of two doses of cannabidiol or placebo, and the number of drop seizures was then recorded by the patients or their caregivers. Blinding is important when the outcome measure is reported by the patient or his or her family or caregivers. Furthermore, in this trial, the outcome measure — the number of drop seizures — could be open to interpretation, particularly in children with a variety of seizure types.

The frequency of drop seizures decreased in all groups, indicating some response in the patients who received placebo. Might the greater reduction in the frequency of these seizures among the patients who were assigned to cannabidiol be related to a failure of blinding owing to side effects or perhaps a difference in the patient's sense of taste or smell? Were the patients' families asked whether they thought their child received cannabidiol or placebo? If so, did a perception of active treatment have any effect on the reported seizure frequency?

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Dr. Poulton reports receiving lecture fees and travel support from Shire and holding shares in GlaxoSmithKline. No other potential conflict of interest relevant to this letter was reported.

1. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *N Engl J Med* 2018;378:1888-97.

DOI: 10.1056/NEJMc1807878

**To the Editor:** Data are lacking to determine whether continuous cannabidiol exposure with or without elevations in liver aminotransferase concentrations is associated with chronic liver injury. Although patients have been treated with cannabidiol for up to 2 years in open-label or uncontrolled studies, studies involving screening for chronic liver injury are lacking.<sup>1</sup>

Elevated aminotransferase levels could indicate an interaction between cannabidiol and valproate at the level of the mitochondria. In addition, data from phase 2–3 trials regarding adverse effects cannot easily address abuse of cannabidiol.<sup>1-3</sup>

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No potential conflict of interest relevant to this letter was reported.

1. FDA briefing document: Peripheral and Central Nervous System Drugs Advisory Committee meeting — NDA 210365: cannabidiol. April 19, 2018

(<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM604736.pdf>).

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DOI: 10.1056/NEJMc1807878

## Correspondence

**The authors reply:** Feng et al. raise the issue of a placebo response in our trial and the possibility that parents may have recognized that their child was randomly assigned to the trial drug because of side effects or a difference in his or her sense of taste or smell. This speculation is relevant to randomized, placebo-controlled trials. However, in this double-blind trial, a matched placebo was used, and a post hoc analysis of the reduction in seizure frequency showed that there was no relationship between the most common side effect (somnolence) and the treatment effect. No other evidence of unblinding was found.

Tampaki et al. suggest that data are lacking regarding the risk of chronic liver injury or slow development of liver fibrosis with long-term exposure to cannabidiol. We agree that formal studies examining long-term hepatic changes related to cannabidiol are lacking. Many antiepileptic drugs are associated with transient and infrequently serious or persistent elevations of hepatic aminotransferase levels.<sup>1</sup> We observed that high initial target doses of cannabidiol, together with elevated aminotransferase concentrations that were above the upper limit of the normal range at baseline and concomitant use of valproic acid or (to a lesser degree) concomitant clobazam, were risk factors for hepatic

dysfunction. We agree that the mechanisms remain

uncertain but may involve reversible mitochondrial dysfunction. Long-term use of cannabis or cannabis-derived drugs containing cannabidiol has not been associated with clinically significant toxic effects in the liver.<sup>2,3</sup> A multicenter study is planned to further assess the potential for chronic liver injury in patients who receive cannabidiol, particularly in those who receive multiple antiepileptic drugs.

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Since publication of their article, the authors report no further potential conflict of interest.

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## Idiopathic Pulmonary Fibrosis

**To the Editor:** In the review article by Lederer and Martinez (May 10 issue),<sup>1</sup> the potential role of statins in the management of idiopathic pulmonary fibrosis (IPF) was not discussed. In a well-defined cohort of 624 patients with IPF, statins were associated with lower risks of hospitalization, disease progression, and IPF-related death than no statin therapy (hazard ratio for death or decline in walking distance, 0.69; 95% confidence interval [CI],

0.48 to 0.99;  $P=0.046$ ).<sup>2</sup> In a registry-based epidemiologic study involving 19,425 patients, Vedel-Krogh et al. found that the hazard ratio for death from any cause among statin users, as compared with patients who had never used statins, was 0.73 (95% CI, 0.68 to 0.79) among patients with interstitial lung disease (analysis based on 5358 patients) and 0.76 (95% CI, 0.62 to 0.93) among patients with IPF (analysis based on 783 patients).<sup>3</sup> In addition to decreasing cholesterol synthesis, the antiinflam

matory, antifibrotic, and immunomodulatory effects of statins have been reported in patients with lung disease and those with cancer.<sup>4-6</sup>

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No potential conflict of interest relevant to this letter was reported.

1. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;378:1811-23.

n engl j med 379;8 nejm.org August 23, 2018 795

The New England Journal of Medicine

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