EDITORIALS

Cannabinoids for Epilepsy — Real Data, at Last

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Medicinal cannabis is a hot-button issue in the treatment of epilepsy. The issue of its use is frequently raised in medical consultations, in the lay press, in social media, and at scientific meetings where the lack of hard data is disheartening. Anecdotal media reports of spectacular results, coupled with the allure of using a "natural" compound and long-held beliefs surrounding its recreational use, plus the fact that medicinal cannabis remains illegal in many jurisdictions, have conspired to make it extremely difficult for physicians to provide advice in this area. That it has been advocated particularly for desperately ill children adds to the societal pressure. Although there have been a few reports of successful treatment with cannabinoids, these have not met standards for clinical trials that provide substantive evidence.[1] The well-known aphorism that "the plural of anecdote is not data" is very applicable here.

There are approximately 100 cannabinoids in the species *Cannabis sativa*, the best studied of which are tetrahydrocannabinol (THC), which is hallucinogenic, and cannabidiol, which is not. The proportions of THC and cannabidiol vary in different plants or chemotypes, and there is a confusing array of legal and illegal preparations with varying proportions of active compounds that are derived from plant extracts or chemical synthesis. Although preparations containing THC may be of value in indications such as pain, multiple sclerosis, or postoperative nausea, preclinical evidence and limited clinical data suggest that cannabidiol, without THC, is the preferred treatment for epilepsy.[1,2] Definitive evidence has been lacking, so the well-performed double-blind, controlled trial of Devinsky et al. in this issue of the *Journal* showing the effectiveness of cannabidiol in the Dravet syndrome is welcome.[3]

Previously, many children with severe epilepsy and intellectual disability did not receive a specific diagnosis; there was only limited ability to take the diagnosis further. With advances in clinical epileptology, genetics, and neuroimaging, specific forms of severe epilepsy that lead to progressive intellectual deterioration can be identified. The Dravet syndrome is one of the best-recognized forms and, in nearly all cases, is due to loss-of-function mutations in the *SCN1A* gene (which encodes the voltage-gated sodium channel alpha-1 subunit), making this a relatively homogeneous clinico-molecular syndrome.[4] *SCN1A* is principally present on inhibitory interneurons; although the details of pathophysiology are still incomplete, at a simple level the Dravet syndrome appears to be due to a lack of inhibition of pyramidal cells, leading to a hyperexcitable state.[5] Children are normal until seizures begin at approximately 6 months of age, often in the context of high fever; seizures become refractory, and by the second year of life, development slows and sometimes regresses. Most of these children are left with a considerable degree of intellectual disability, ongoing seizures, and a serious risk of early death. Treatment is challenging, and it is rare for a patient with the Dravet syndrome to become seizure-free.[4]

Devinsky et al. found a significantly greater reduction in seizure frequency among patients who received cannabidiol than among those who received placebo, and the seizure-free rate was 5% with the active drug as compared with 0% with placebo. Thus, anecdote has been confirmed by data, and one might ask whether a controlled trial was really necessary. The answer is absolutely yes. Perhaps counterintuitively, the rate of response to placebo in clinical trials is higher among children than among adults.[6] Moreover,

parents who go to enormous efforts to get cannabis for their children report a higher response rate than those who can easily obtain it.[7] Cannabidiol is not without side effects. The dropout rate in the active-treatment group was appreciable, and common side effects included vomiting, loss of appetite, and diarrhea. With additional experience, perhaps these effects can be modified with dose adjustment and other strategies.

A major aim in the field of the Dravet syndrome and other genetic encephalopathies is to develop precision therapies — treatments directed at the specific genetic defect.[8] Because the Dravet syndrome has a single-gene basis, it is an attractive target for precision medicine.[8] However, cannabidiol is not a precision treatment for the syndrome, because there is no established link of the cannabinoid receptors with the inhibitory interneuron pathology of the Dravet syndrome, and the response across the cohort of the current study was not uniform.

This trial represents the beginning of solid evidence for the use of cannabinoids in epilepsy. It requires replication. Future trials may answer further questions about the applicability of cannabinoids to the many other syndromes of childhood epilepsy and to treatment in adults. After an era dominated by anecdote and obfuscated by medicolegal issues and emotionally infused debate, more scientific studies are under way. Much more research is needed to understand the basic science, benefits, and risks of cannabinoids in epilepsy.

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

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Levosimendan for the Low Cardiac Output Syndrome after Cardiac Surgery

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The low cardiac output syndrome complicates 1 in 10 coronary bypass operations and is associated with a heightened risk of perioperative death.[1] The pathophysiology of this syndrome is complex, with likely contributions from reperfusion injury, systemic inflammation induced by cardiopulmonary bypass, and pulmonary and systemic vasoconstriction.[2]

Pharmacologic management of the low cardiac output syndrome typically includes positive inotropic drugs such as beta-adrenergic agonists and phosphodiesterase inhibitors. Although these agents may increase cardiac output, they also heighten the risk of atrial and ventricular arrhythmias, and they may exacerbate myocardial ischemia by increasing myocardial oxygen consumption. In two observational studies, patients receiving perioperative inotropes had higher rates of postoperative myocardial infarction, stroke, renal dysfunction, and in-hospital death than those not receiving inotropes.[3,4]

Levosimendan is a calcium-sensitizing agent with a mechanism of action that is distinct from those of other inotropes and with a prolonged duration of action.[5] By stabilizing the binding of calcium to troponin C, levosimendan enhances actin–myosin cross-bridging and increases contractile force. It also acts as a vasodilator by means of an effect on ATP-sensitive potassium channels in vascular smooth muscle. Since levosimendan acts without enhancing intracellular concentrations of free calcium, it does not increase myocardial oxygen demand. Although levosimendan is not approved by the Food and