VIEWPOINT

The Achilles Heel of Medical Cannabis Research—Inadequate Blinding of Placebo-Controlled Trials

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Interest in medical cannabis in the United States has increased rapidly in the past 5 years, and now it is legal in 29 states and the District of Columbia. The evidence base to support the use of medical cannabis has developed too, albeit more slowly. For instance, there have been numerous randomized clinical trials that have evaluated the effectiveness of smoked or vaporized cannabis, as well as targeted trials of its principal cannabinoids, tetrahydrocannabinol (THC), and cannabidiol (CBD).[1] Some of the strongest evidence is for neuropathic pain, spasticity associated with multiple sclerosis, and anorexia in the setting of serious illness. On the other hand, other common conditions for which cannabis is often used, such as posttraumatic stress disorder, so far have very little evidence of benefit.

Although there is growing acceptance of medical cannabis as a legitimate therapy, this acceptance has been driven by placebo-controlled trials that are flawed by inadequate blinding. This flaw, in turn, biases studies to overestimate the effectiveness of medical cannabis. Without careful attention to this limitation, there is a very real risk that physicians and patients will misinterpret the results of these studies, and see benefits that do not exist.

Failures of Blinding in Medical Cannabis Research

In clinical trials of smoked or vaporized medical cannabis, the placebo arm typically uses inactive cannabis. These are flowers from which cannabinoids have been extracted, often with liquid carbon dioxide. This "placebo" cannabis is indistinguishable in appearance, taste, and odor from natural cannabis.

Nevertheless, many trial subjects can distinguish between active cannabis and placebo. For instance, in one placebo-controlled crossover trial of cannabis for pain,[2] participants were given cannabis cigarettes containing 8% THC or placebo cigarettes, separated by a 2-week washout period. Of 28 participants, almost all of those who were assigned first to active treatment guessed their treatment assignment correctly (14 of 15 [93%]). Of the participants who received placebo cannabis first, only 5 of 13 (38%) guessed correctly, but almost all (12 of 13 [92%]) guessed correctly when they crossed over to active cannabis.

These participants guess their group assignment in large part because they detect the psychoactive properties of the active cannabis treatment. That is, the design of the study provides inadequate blinding. This is evident in a similar crossover study of medical cannabis for pain, in which participants received cannabis cigarettes that contained high-dose cannabis (7.5% THC), low-dose cannabis (3.5% THC), and placebo cannabis.[3] The 32 participants who completed all 3 groups in random order reported greater feelings of being "high" and "stoned" in the high-dose group than in the low-dose group, and both THC groups scored higher than the placebo did. Similarly, perceptions of feeling "sedated" or "impaired" were significantly higher in the active groups than the placebo group.

In a clinical trial, lack of blinding can lead subjects to overestimate beneficial effects. Conversely, participants who believe they are receiving the active drug might be more alert to adverse effects. Together, these effects should raise substantial concerns about the validity of medical cannabis trials.

Approaches to Improve Blinding

There are at least 4 ways that randomized clinical trials of medical cannabis could be designed to reduce this bias, or at least to make the magnitude of that bias more apparent. First, trials could include a psychoactive control. This approach has a long history that began with a study of the effects of psilocybin on religious experience in the Marsh Chapel Experiment,[4] so-called because it was conducted in Boston University's Marsh Chapel on Good Friday. That study used niacin, in hopes that its acute flushing reaction would convince some subjects to believe that they had been given psilocybin.

Unfortunately, it is not clear what an ideal psychoactive control would be in a cannabis trial. Any drug would need to mimic some of the most prominent effects of cannabis, including an elevated heart rate and dry mouth, as well as euphoria. And, of course, any drug should not have any direct clinical effect on the symptom or condition that is the study's primary end point. Anticholinergic drugs like atropine might be used to induce physical symptoms of dry mouth and tachycardia, and benzodiazepines could produce sensations of relaxation resembling the euphoria of cannabis. Neither anticholinergic drugs or benzodiazepines, however, can easily be administered by smoking or vaporizing.

Second, participants for trials could be recruited who are naive to cannabis use. It is likely, although not certain, that participants who are unfamiliar with the effects of cannabis would be less able to accurately determine whether they are receiving cannabis or a placebo. There are risks of this approach, however. Many clinical trials of medical cannabis, like the study by Wilsey and colleagues,[3] recruit participants who are experienced in medical or recreational cannabis use to minimize the incremental risks of addiction or new adverse effects.

Third, trials at a minimum could assess the adequacy of blinding. Questions could assess beliefs about treatment assignment, as in the study by Ellis and colleagues,[2] and they also might assess subjective sen-

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sations of physiologic and psychological effects, as in the study by Wilsey and colleagues.[3] Although such questions cannot eliminate bias, they allow for a post hoc evaluation of bias and can help to guide the interpretation of trial results.

Finally, clinical trials can explore cannabis strains and preparations that are enriched for CBD, which does not have the psychoactive effects of THC. One study of CBD in doses of 600 mg orally found none of the euphoria or "stoned" feeling that THC causes.[5] This approach, however, raises different challenges. Currently in the United States, the only approved source of cannabis for medical research is from the University of Mississippi Marijuana Research Project.[6] Although that single-source arrangement allows for a high degree of standardization and quality control, it also severely limits the ability of growers to respond to researcher requests for tailored strains of cannabis. So unless additional sources of cannabis for medical studies become available, researchers who want to use CBD-predominant strains or other formulations (eg, oils, tinctures) may find their options are very limited.[7]

Next Steps

Until the problem of inadequate blinding is solved, there is a very real risk that clinical trials of medical cannabis would overestimate its benefits. This risk is concerning, especially because the evidence base to support the use of medical marijuana has not kept pace with growth in its legalization.[1] And many of the existing trials are flawed.

Other obstacles to medical cannabis research compound these methodological challenges. For instance, now that patients can more easily obtain medical and recreational cannabis, they may have little incentive to enroll in a trial. The limited cannabis strains available through the University of Mississippi's farm, and a relatively modest "cap" on THC concentration (13%), mean that clinical trials must be designed around available strains. Finally, researchers also face regulatory barriers to research and must work around a lack of federal funding.

As more research is conducted, the evidence base is likely to catch up, reinforcing some uses of medical cannabis and rejecting others. An important step in promoting research could be the Marijuana Effective Drug Studies Act,[8] recently introduced in the Senate, which would increase investigator access to marijuana, and reduce regulatory barriers to clinical research. Until then, patients and physicians should use caution in interpreting the results of clinical trials of cannabis and should be skeptical about benefits that are reported.

ARTICLE INFORMATION

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