Evidence-Based Medicine versus Medicinal Cannabis

By Jack D. McCue MD

At the end of 2016 a simple search in PubMed (the online US National Library of Medicine at the National Institutes of Health) with the criteria “cannabis or cannabinoids or marijuana” identified 40,000 citations in bioscientific journals and books, dating back to 1846. The total number of citations is growing by about 3,000 each year with a shrinking doubling time of seven years.

Most of the cited papers are trivial, dated, and ill-informed, and many are polemics by ignorant editorialists irrevocably drawn to cute titles such as “Medical Marijuana: All Smoke and Mirrors.” But there are thousands of serious scientific papers, some providing profound insights into the functioning of the most important signaling system in the mammalian body, and irrefutable documentation of the medical benefits of cannabinoids and terpenes.

The challenge for the doctor is how to find the useful and reliable published material out of the 40,000 candidates. Evidence-Based Medicine (EBM) to the rescue? Regrettably, not yet.

What is Evidence-Based Medicine? Beginning in the 1960s, an interest in how physicians made decisions developed into a scholarly discipline that employed insights from sophisticated statistical analyses, clinical epidemiology, epistemology, psychology, and history.

The pioneers of Evidence-Based Medicine include David Eddy (who first used the term “evidence-based medicine” and developed much of its methodology), Alvan Feinstein (who popularized Venn diagrams —see graphic above), Archie Cochrane (who devised a ranking system for quality of design in published papers), and David Sackett (who developed the first systematic reviews, clinical epidemiology, epistemology, and credibility with doctors and politicians).

The core methodology of Evidence-Based Medicine (EBM) aims to use the best evidence available to answer a clinical question. This evidence is based on randomized controlled trials (RCTs) that directly assess the effect of an intervention on patient outcomes. EBM is based on the scientific method, which involves formulating a hypothesis, designing a study, collecting data, analyzing the data, and drawing conclusions.

The EBM analysis was funded by the National Institutes of Health in an effort to provide evidence-based decision-making for the treatment of diseases such as cancer. The study was designed to determine the effectiveness of a particular intervention, such as chemotherapy or surgery, compared to other treatments. The results were published in the Journal of the National Cancer Institute.

The EBM approach is considered the gold standard for medical decision-making because it relies on rigorous scientific evidence. It is based on the principles of evidence-based medicine, which are principles that have been developed and refined over the past few decades.

Evidence-based medicine is a way of thinking that emphasizes the importance of evidence in making clinical decisions. It is a process that involves gathering and analyzing evidence from research studies and using that evidence to make informed decisions about patient care.

There are many different types of evidence that can be used in evidence-based medicine. These include randomized controlled trials, systematic reviews, meta-analyses, case studies, and expert opinions.

Evidence-based medicine is different from other approaches to medical decision-making because it is based on the best available evidence. This means that it is not based on personal opinions or biases, but rather on research studies that have been conducted in a rigorous and systematic manner.

Evidence-based medicine is not a replacement for clinical judgment, but rather a tool that can help doctors make more informed decisions. It can help doctors avoid common mistakes, such as treating patients with ineffective or harmful treatments.

Evidence-based medicine is also important for ensuring that patients receive the best care possible. It is based on the idea that all patients should receive the same treatment if they have the same condition, regardless of who their doctor is or where they live. This is called patient-centered care.

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point that people who buy vitamins are in a higher socioeconomic group and are less likely to smoke tobacco, and that is why they live longer.

Or, if the drug being tested is a harsh synthetic like Marinol, failure to demonstrate statistically significant results may be related to the poor choice of the intervention itself or poor dosing. And as Ethan Russo has pointed out, the placebo effect in cannabis studies is large and growing, and the benefits actually provided by cannabis are influenced by patients' expectations that it will be very effective. EDIT

Turning to statistically flawed studies is sometimes surprisingly helpful. For one thing, the researchers behind weaker studies usually know more about cannabis than those behind the FDA-ready studies. Let's look at some examples of weak studies that reached the correct conclusions, but could never aspire to the standards of EBM.

Migraine. As any doctor who has monitored cannabis use by migraine-sufferers can tell you, it works —often dramatically. Yet until a few months ago there were no human studies to validate or deny those anecdotal reports.

DN Rhyne and colleagues in the family practice program at the University of Colorado recently published a retrospective chart study of 121 patients (unfortunately, statistically speaking, out of 262 patients they identified). They found that use of cannabis was associated with a reduction in migraine episodes by more than half (with one chance in a thousand that their results could be a random outcome). Methodologically, this study had so many design flaws that it would reduce an EBM researcher to tears. But not only is it the only study in the medical literature, it just happens to be correct —without a doubt.

Conclusion #1: Just because a study is poorly designed and executed does not mean that it is wrong. If it is all you have, and the intervention is relatively harmless, cannabis may be worth a try. If it works... it works!

Insomnia. Studies of cannabinoids in insomnia barely made it past the lowest standard of EBM ("very low" reliability). The JAMA meta-analysis found only two insomnia studies worthy of inclusion in their meta-analysis (14 of which were Sativex trials which generally have decent study designs). This review properly concluded that the human studies of medical cannabis and insomnia varied greatly in design and were generally of poor quality. In one pathetically bad study, 30 mg of Marinol (!) was given to two insomniacs for 14 nights. Its effect on sleep was "poorly understood," the authors concluded.

EDIT

Table 2: Summary of Studies Evaluated in a Meta-Analysis of Placebo-Controlled Trials and Results for Primary Outcomes: Included or Excluded Studies...
Overall, the comprehensive review concluded that while the study outcomes were highly variable, when a consistent measurement tool for insomnia was used, the results were more consistent. Duh.

Never considered in either of the reviews were the alternative treatments for insomnia. Zolpidem (Ambien) has bizarre and dangerous adverse effects that have landed insomniacs in jail, and is a drug that reliably induces durable dependence. Benzodiazepines cause mental numbness and hangovers, and reliably result in dependence.

Low doses of the antidepressant amitriptyline result in lingering drowsiness—and can cause fatal overdoses; antihistamines and melatonin simply don't work. Set in context with this collection of losers, the cannabis studies look rather promising!

Conclusion #2: If the alternatives are dangerous and ineffective, analyzing the quality of the studies that concluded that cannabis might be effective is kind of beside the point. It is worth a try until more statistically convincing studies find it to be ineffective. And the fact is, for a substantial minority (maybe about 30%), it does work well when all the other options have failed.

Cancer. It is incontrovertibly true that cannabis is effective for many of the symptoms of cancer (pain, appetite loss) and side effects of cancer treatments (nausea and vomiting, painful neuropathy). And it is almost certainly helpful for many other associated secondary symptoms (anxiety, insomnia, depression, feelings of hopelessness). But does it actually treat the malignancy itself?

The complexity of this seemingly simple question is beyond daunting. There may not be reliable answers to this question for decades, if then. The anecdotal experiences of malignancies that have improved or been cured can be powerfully persuasive, but they also can be incorrect. Still, a patient with an unresectable glioblastoma has less than a coin-flip chance that he or she will live more than a few months. As long as treatment with cannabis does not interfere with the treatment of the cancer itself (and there are legitimate concerns for some cancers), what do you have to lose?

The most secure recommendation is that if cannabis can be used to treat symptoms of the cancer or the chemotherapy effectively, arguments against trying to use it as possible treatment of tumor look rather thin. Unfortunately, the question then becomes “Well, if I am hoping for an anti-tumor effect, how do I use it?” The answer to that question is simply unknown. (Joe D. Goldstein, MD, confronts it on page 25 of this issue.)

Conclusion #3: Lack of good studies notwithstanding, if you are running out of treatment options, have little or nothing to lose, and the risk of harm is low, why not try it?

Inflammatory Bowel Disease (IBD). Conventional treatments of IBD (predominantly ulcerative colitis and Crohn’s disease) work for most patients, but a relatively small percentage of cases are resistant to treatment, or patients cannot tolerate (or afford) some of the most effective therapies. In an informal pilot study, Hergenrather documented that patients with IBD clearly believe that cannabis relieves symptoms, improves quality of life, and allows them to discontinue some of the toxic drugs routinely used for treatment.6

There is also a series of small studies by Timna Naftali and colleagues in Israel who strongly assert that (plant) cannabis treatment is effective, including one that is a credible RCT. Unfortunately, all the studies are small, highly susceptible to bias, and illustrate several of the barriers to high quality cannabis RCTs pointed out by Russo.

Nonetheless, anecdotal experiences of success with self-treatment of IBD with cannabis, such as Hergenrather’s, are consistent with the recent Israeli RCT showing complete remission in five of 11 patients, complete weaning of corticosteroids in three, and statistically significant improvement in appetite, sleep, and quality of life. A follow-up, larger study has been initiated, but these small studies are all we have for the near future. They probably would not have made the JAMA meta-analysis. The JAMA meta-analysis included IBD among its diagnoses, as it should have. But neither can they be ignored.

Conclusion #4. Pretty good research just has to be good enough while we wait for statistically solid studies to be done. The irrational block to legitimate cannabis research must be removed so good RCTs can be done.

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In summary, EBM’s standards are goals for clinical researchers who are objectively examining medical benefits of cannabis to strive for. Under-funded, ill-designed studies carried out under siege by government agencies can hardly meet those standards. Until the obstacles to good research are removed, the scientific community must ask whether the EBM-style criteria that work for pharmaceutical research are the best way to evaluate plant-based therapies. Doctors and researchers must learn how to use plant cannabis with proper dose titration and reliable delivery systems before statistically solid studies to be done. The needed clinical trials will emerge slowly, and most research results will continue to be frustratingly inconsistent. That does not excuse us from doing the best with what we have, for the benefit of our patients who need our help now.

References:

Medical Letter Lists a Few Indications for Cannabis

For the first time in its 57-year history, the influential, proudly independent Medical Letter on Drugs and Therapeutics, summarized its views on the uses for “Cannabis and Cannabinoids.” Physicians depend on the Medical Letter—which is regularly republished in JAMA— for unbiased reviews of clinical trials on specified drugs, categories of drugs, or disease groups, presented with a methodological rigor that preceded the development of the techniques of Evidence-Based Medicine.

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The Medical Letter listed chemotherapy-induced nausea and vomiting, pain and spasticity in multiple sclerosis, and epilepsy as the only medical indications for use of cannabinoids (botanical marijuana) that have good support from randomized clinical trials (RCTs). Its summary was, in fact, a reiteration and reduction of the 2015 paper by Whiting et al, adding only the recent trials of Epidiolex in epilepsy. No original analysis or guidance for physicians was added.

As predicted byMcCue in the accompanying article, the meta-analysis by Whiting et al evidently influenced and limited the discussion. The clinical indications for cannabis discussed in The Medical Letter were even more limited. The potential value of using plant-based cannabis was dismissed in the categorically incorrect final sentence: “No adequate studies of cannabis (botanical marijuana) are available for any of these indications.”

McCue comments, “My guess is that they did not even bother to look beyond the preceding JAMA article, and accepted the conclusions of Whiting, et al without a critical review of its methodology and implications of its conclusions.”