Evidence-Based Medicine vs. Medicinal Cannabis

By Jack D. McCue MD

At the end of 1988 a simple search in PubMed (the online US National Library of Medicine at the National Institutes of Health) with the criteria “cannabis or cannabinoid or marijuana” will turn up more than 38,000 citations in bioscientific journals and books, dating back to 1846.

The total number of citations is now growing by more than 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 editorials irresistibly drawn to cute titles such as “Medical Marijuna: All Smoke and Mirrors?” or “High Time for Science-Based Medicine.”

But there are many thousands of serious scientific papers, some providing profound insights into the functioning of the most important systems of the body, the brain, and the immune system, 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 from thousands of clinical studies from dozens of countries written over the past century.

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 behavioral science.

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 program in clinical epidemiology at McMaster University).

My brush with EBM began in the early 1970s at Beth Israel Hospital and the Harvard Community Health Plan. Anthony O’Shaughnessy, a former part-time job in rural Northern California and a fellow of the American College of Physicians and the American Geriatrics Society, led a group of physicians who, believing that evaluation and in some cases, treatment, of common complaints (for example, urinary tract infection, cough, chest pain) could be reduced to binary decisions (yes-no answers on a check-box practice guideline template), and each was graded by a rigorous assessment of the evidence.

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He has led the group of over 100 people in the development of evidence-based algorithms for primary care clinical decision-making at Harvard Medical School. “Mandated use of such algorithms plagues physicians to this day,” he notes.

Hence, evidence-based medicine. The required algorithms are to be used to coordinate nurse practitioners and physician assistants to handle minor problems and triage more complex ones for physician evaluation. Or at least that was the idea.

Unfortunately, clinicians still consistently preferred to use their own clinical judgment. Me, too.

At its best, evidence-based medicine merges scientific research findings with clinicians’ best medical judgment based on their experience and what the patient is seeking from their medical care.

Of course, it doesn’t work that way. Perhaps, inevitably, the techniques of decision analysis, meta-analysis (which employs statistical methods to combine the patient numbers and results of disparate clinical trials into a single, more powerful conclusion), and systematic reviews of the medical literature moved away from analyses designed to be helpful to practitioners, and progressively began to emphasize the mechanics of EBM—the statistical play- ground of PhDs rather than clinicians.

Cannabis has been spared the cold analytical glare of EBM until recently. There were simply not enough randomized clinical trials (RCTs) to analyze.

Input of physician judgment was systematically avoided being unreliable. (The PhDs do have their point, but medi- cal practice would be paralyzed if we could only make decisions based on presumed-reliable analytics produced by PhDs.)

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That changed, for better or worse, in June 2015, when “Cannabinoinds for Medical Use: A Systematic Review and Meta-analysis” by Whiting et al was published in the Journal of the American Medical Association.

The meta-analysis found that for two conditions—chronic pain and spasticity due to multiple sclerosis—there was at least moderately good evidence of medical effect- iveness of cannabinoids and cannabis.

(See table on next page.)

The authors concluded that the evidence supporting effectiveness of cannabinoids was stronger for treatment of nausea and vomiting, HIV/AIDS, sleep disorders, anxiety, de- pression, psychosis and Tourette syndrome was credible, but weak or very weak.

This was the only nearly-comprehensive EBM paper of the cannabis literature using proper meta-analytic techniques, and doctors and politicians gave it more credi- bility than it deserved. As an indication of how often it has been used to summarize clinical research, the landmark report of the National Academy of Sciences, Engi- neering, and Medicine (NAS) released in 2017 referenced Whiting et al on 21 occasions.

It does, however, provide “exhibit A” in our argument of whether EBM currently offers the best techniques for analyzing the clinical evidence for the widely held be- liefs by cannabis users that it is effective for treatment of a large number of medical conditions.

Cannabis is being widely used in the treatment of many more than 10 conditions.

The Whiting EBM analysis was fund- ed by the Swiss Federal Office of Public Health, which determined the 10 diagnos- es to be studied. Cannabis is being widely used in the treatment of many more than 10 conditions, and from the clinician’s per- spective, it would be helpful to assess the relevant literature on all of them. The prob- lem is a lack of adequate RCTs for EBM.

The choices by Whiting et al were not necessarily bad ones, but EBM is only as useful as the topics chosen for exami- nation. It is not clear why only 10 condi- tions were reviewed, or why those 10 were chosen. (Oddly, they included glaucoma, which has no RCTs to analyze.)

For example, migraine, epilepsy, opioid dependence, stress, and ibnmycolatosa has a useful supporting medical literature — but no solid RCTs. A few others, such as inflammatory bowel disease do have per- suasive small RCTs and would have have earned a weak or very weak rating.

But the core methodology of EBM is that only RCTs are taken as serious data. Un- less the study is an RCT, the best EBM will give it is a low or very-low quality rating — if that. EBM excludes non-clinical stud- ies (animal or lab studies), which is appropriate, because drugs should not be used based on non-human studies. Thus 99.7% of the scientific articles that the authors included in their review analysis were discarded. Stating it differently, the entire analysis was based on only 79 out of 7,561 articles they identified.

In the JAMA paper by Whiting et al, nearly all the RCTs that made it through the screening criteria were pharmaceutical company trials or used synthetic CBD and THC — very few used what our patients actually use—herbal Cannabis.

And no experienced cannabis clinician thinks that a single synthetic cannabinoid molecule can replicate the beneficial “en- tourage” effects of the cannabis plant. At least one Israeli RCT confirms the superior efficacy of THC-rich whole-plant extracts in the treatment of IBD, and CBD-rich ex- tracts were strikingly superior to purified CBD in multiple preclinical studies.

Trying to corral messy plants like canni- bas into the tight, transparent boundaries of the randomized placebo-controlled clin- ical trial in humans is harder — and harder to find funding for— than studying a syn- thetic single molecule in rats. Ethan Russo has concisely summarized the barriers to clinical research encountered when the ac- tive medication being tested is botanical cannabis. (See box at bottom of page.)

Seven of eight studies on pain deemed “adequate” by the JAMA authors were Sativex trials.

Most drug studies that meet the stringent requirements for inclusion in EBM are ones aimed at the FDA drug approval process. Seven of eight studies on pain deemed “adequate” by the JAMA authors were Sativex trials. All six studies on spasticity were either Sativex (four), Marinol, or a con- gestion of synthetic THC and CBD. Sativex is constituted as a whole-plant extract of multiple cultivars, but even the basic stud- ies needed to demonstrate Sativex’s equiv- alency with whole-plant smoke or vapor in humans have not been performed — and it may not be.

Even when EBM is done well, there is room for interpretation and the results may not agree with other EBM reviews. Hence, recommendations based on seemingly reli- able RCTs may differ widely.

Post-traumatic stress disorder (PTSD) is an apt example, in part because it is a disabling problem for which cannabis is obviously superior to other therapies. (For shame, VA.) A careful, clear-eyed com- mentary on the conflicting practice guide- lines for treating PTSD drawn up by six august medical bureaucrats and profes- sional bodies, all of which were supposed- ly based on a systematic review of all available RCTs, stifled: “It is notable that all of these (of conflicting) reports are es- sentially reviews of the same research but have drawn different conclusions.”

Are There Alternatives to EBM?

For the minority professor who has spent a 40+ year career educating students and post-graduate medical resi- dents in evidence-based clinical decision-making (not to mention decades as a CMO, using EBM to berate the poor surgeons to cut costs) fails his retirement. In an at- tempt to avoid getting stigmatized, I took a part-time job in rural Northern California advising more than 3,000 cannabis-using...
patients—nearly all of whom, incidentally, grow their own weed and know an awful lot about cannabis (in dramatic contrast to the doctor-professor who knew nothing at all).

Seriously! I had never heard of THC or CBD, and I thought my neighbor in Marin County had a bad skunk problem. Well, the first thing you do is a lot of quiet listening, and you learn the humility it takes to be taught by knowledgeable salt-of-the-earth people, many of whom had not made it through high school. And you quickly learn that the medical literature on cannabis is shallow and terribly biased, and that the seemingly authoritative researchers are actually as ignorant as I was.

My instinct, turning to EBM for knowledge and thoughtful answers, was a joke. EBM is a very powerful, necessary tool for making sense out of an overwhelming amount of often conflicting data, but it is only as good as the studies it analyzes. For example, just because the data from a well-designed study shows statistically significant differences does not mean that it is medically correct. There may be hidden flaws in the study design. Let's say you discover that people who take vitamins live longer. But unfortunately you have not considered the possibilities that people who buy vitamins are in a higher socioeconomic group or maybe people who take vitamins 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 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.

Another (preferable, but still flawed) option is the "systematic review," which attempts to avoid some of the serious shortcoming of EBM. The systematic review process is exemplified by the impressive NAS publication (468 pages!), "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research," which was designed to be a comprehensive review of the literature by panels of 31 experts supported by a large staff of research associates and clerical assistants, plus some 800 experts overseeing it all.

The staff and experts determine which scientific articles are worthy of review with more of an "inclusive" process based on potential relevance of content of articles, rather than the "exclusive" process of

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Table 2: Summary Estimates from Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes with Associated GRADE Ratings

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of Patients (No. of Studies)</th>
<th>Cannabis (No. of Studies)</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Summary Estimate</th>
<th>GRADE Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>1 (66)</td>
<td>Nabilomide</td>
<td>Placebo</td>
<td>Depression</td>
<td>RR = 0.85 (0.69 to 1.05)</td>
<td>Low</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (24)</td>
<td>Cannabis (7)</td>
<td>Placebo</td>
<td>Anxiety</td>
<td>RR = 0.71 (0.56 to 0.91)</td>
<td>Low</td>
</tr>
<tr>
<td>Substance</td>
<td>1 (27)</td>
<td>Cannabis (7)</td>
<td>Placebo</td>
<td>Substance</td>
<td>RR = 0.80 (0.65 to 0.99)</td>
<td>Low</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (33)</td>
<td>Cannabis (7)</td>
<td>Placebo</td>
<td>Pain</td>
<td>RR = 0.70 (0.52 to 0.95)</td>
<td>Low</td>
</tr>
<tr>
<td>Sleep</td>
<td>1 (17)</td>
<td>Cannabis (7)</td>
<td>Placebo</td>
<td>Sleep</td>
<td>RR = 0.70 (0.52 to 0.95)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: ADL, activities of daily living; CBD, cannabis based medicine; EQ-5D, Euroqol Five Dimension Scale; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NRS, numerical rating scale; OR, odds ratio; THC, tetrahydrocannabinol; VAS, visual analog scale; WMD, weighted mean difference.

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Studies included in the meta-analysis by Whiting et al in JAMA are summarized with outcomes and resulting quality of shown in column at right. Abbreviations: ADL, activities of daily living; CBM, cannabis based medicine; EQ-5D, Euroqol Five Dimension Scale; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NRS, numerical rating scale; OR, odds ratio; THC, tetrahydrocannabinol; VAS, visual analog scale; WMD, weighted mean difference.
Lack of good studies to manifest a flashpoint. By varying the focal length, it works!

"Evidence-Based Medicine" pens to be correct —without a doubt.

...dotal reports.

...man studies to validate or deny those anecdotal examples of malignancies that have undergone treatment, little or nothing to lose, and the risk of harm is low, why not try it?

"LAMOTRIGINE BLOOD (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 a landmark pilot study, Herzallah and colleagues 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.

There is also a series of small studies suggesting that Nabilone and derivatives in cancer patients who strongly assert that (plant) cannabis treatment is effective, including one that is a credible RCT. Unfortunately, all these studies are small, highly susceptible to bias, and illustrate several of the barriers to high quality cannabis RCTs pointed out by the letter.

Nevertheless, anecdotal experiences of success with self-treatment of IBD with cannabis, such as Herzallah’s, are not uncommon. The recent systematic 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 now. They probably would not have made it past the exclusion criteria, even if the JAMA meta-analysis had included IBD among its diagnoses, as it depicts the letter.

Nevertheless, according to the current preclinical research on the bell-shaped dose-response of cannabidiol by Kuhar, Dubery, and Grotenhermen.

The bell-shaped dose-response of cannabidiol by Kuhar, Dubery, and Grotenhermen indicated that low doses of the antidepressant amitriptyline were effective for many of the symptoms of depression and anxiety, while high doses and sometimes in low doses were not.

One of the first in its 57-year history, the influential, proudly independent Medical Letter (on Drugs and Therapeutics), summarized its views on the uses for "Cannabis and cannabidiol in cancer patients." We are pleased to report in this issue of the Medical Letter, issued in conjunction with the recent and well-documented studies of cannabis and cannabinoids in the treatment of cancer.

The Medical Letter is the most widely read publication in the world on the efficacy and safety of cannabis and cannabinoids in the treatment of cancer. We are pleased to report in this issue of the Medical Letter, issued in conjunction with the recent and well-documented studies of cannabis and cannabinoids in the treatment of cancer.

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