'Evidence-Based Medicine' vs. 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.

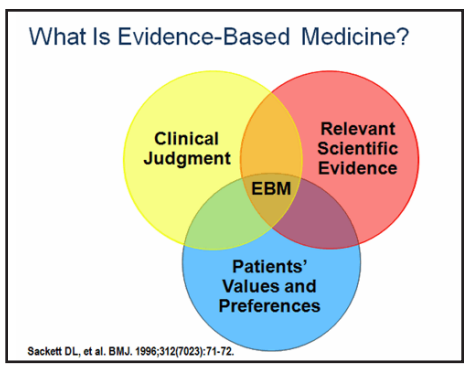
The total number of citations is growing by about 3,000 each year with a shrinking doubling time of seven years.

Most of the cited papers are trivial, dated, and ill-informed, and many are polemics by ignorant editorialists irresistibly 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.



Venn Diagram depicts the ideal of EBM (Evidence-Based Medicine) incorporating elements of Clinical Judgment, Relevant Scientific Evidence, and Patients' Values and Preferences.

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 economics.

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 Kamaroff, MD, the leader of our research group, believed that evaluation and in some cases, treatment, of common complaints (for example, urinary tract infection, cough, chest pain) could be reduced to binary decisions, each of which would be supported by assessment of the evidence. The resulting algorithms could be used by nurse practioners and physician assistants to handle minor problems and refer more complex ones for physician evaluation.

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

At its best, Evidence-Based Medicine merges scientific 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 literature moved away from analyses designed to be helpful to practitioners, and began to progressively emphasize the statistics and mechanics of EBM —the playground of PhDs rather than MDs. Physician judgment was systematically avoided as being unreliable. (The PhDs do have their point, but medical practice would be paralyzed if we could only make decisions based on presumed-reliable data).

Cannabis has been spared the cold analytic glare of EBM until recently. There were just not enough randomized clinical trials (RCTs) to analyze. That changed, for better or worse, in June 2015, when "Cannabinoids for Medical Use: A Systematic Review and Meta-analysis" by Whiting et al was published in the Journal of the American Medical Association.[2]

The meta-analysis found that for two diagnoses — chronic pain and spasticity due to multiple sclerosis— there was at least moderately good evidence of medical effectiveness of cannabinoids and cannabis. *(See illustration on next page.)*

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

This is the only nearly-comprehensive EBM paper of the cannabis literature using proper meta-analytic techniques, and it will undoubtedly have much more prominence and credibility with doctors and politicians than it deserves.

The core methodology of Evidence-Based Medicine is that only RCTs are taken seriously.

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

The EBM analysis was funded by the Swiss Federal Office of Public Health, which determined the 10 diagnoses to be studied. Cannabis is being widely used in the treatment of many more than 10 conditions, and from the clinician's perspective, it would be helpful to assess the relevant literature on all of them. The problem is a lack of adequate RCTs for EBM.

99.7% of the scientific articles that the JAMA authors' literature search uncovered were discarded!

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

The choices by Whiting et al were not necessarily bad ones, but EBM is only as useful as the topics chosen for examination. EDIT It is not clear why only 10 conditions were reviewed, or why those 10 were chosen. Oddly, they included glaucoma, which has no RCTs to analyze and for which the usefulness of cannabis is very limited.

The core methodology of EBM is that only RCTs are taken seriously. Unless your study is an RCT, the best EBM will give it is a low or very low quality rating —if that. EBM excludes non-clinical studies (i.e., 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 JAMA authors' literature search uncovered were discarded! The entire analysis was based on only 79 out of the 23,754 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 —not herbal *Cannabis*.

No experienced cannabis clinician thinks that a single synthetic cannabinoid molecule can replicate the beneficial "entourage" effects of the cannabis plant. And at least one Israeli RCT[9] confirms the superior efficacy of whole-plant extracts in the treatment of IBD.

Trying to corral messy plants like cannabis inside the tight, transparent boundaries of the randomized placebo-controlled clinical trial is harder —and harder to find funding for— than studying a synthetic single molecule in rats. Ethan Russo has concisely summarized the barriers to clinical research encountered when the active medication being tested is botanical cannabis. *(See box at bottom of page.)*

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 concoction of synthetic THC and CBD.

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 reliable 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 commentary on the conflicting practice guidelines for treating PTSD drawn up by six august medical bureaucracies and professional bodies, all of which were supposedly based on a systematic review of all available RCTs, sniffed: "It is notable that all of these (conflicting) reports are essentially reviews of the same research but have drawn different conclusions."[4]

Are There Alternatives to EBM?

What happens when the crusty professor who has spent a 40+ year career educating students and post-graduate medical residents in evidence-based clinical decision-making (not to mention decades as a CMO, using EBM to berate the poor surgeons to cut costs) fails retirement? In an attempt to avoid going stir-crazy, 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 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. The EBM-worthy research wasn't there, and what was there was almost always unhelpful. (*Dumb* was the first adjective that came to mind.).

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. For example, if you discover that people who take vitamins live longer, you may have missed the

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Barriers to high quality cannabis RCTs*

Variable cannabinoid/terpene content among chemovars
Unreliable cannabinoid/terpene content among single chemovars
Capricious naming of chemovars
Lack of standardized delivery systems
Wild and irrational variation in state and federal regulations
Wide variation in individual expressions of endocannabinoid tone
FDA regulatory hurdles to approval of any botanical medication
Uncertainties surrounding interactions among cannabinoids/terpenoids (e.g. entourage effects)
Pronounced (and growing) placebo effects in cannabis trials
Difficulty in blinding RCTs because of psychoactivity of cannabinoids/terpenoids
Complexities of necessary dose titrations and adjustments for tolerance development
Uncertainty in necessary length of clinical trials to detect delayed efficacy

*Somewhat adapted from EB Russo Current therapeutic cannabis controversies and clinical trial design issues. Front Pharmacol 2016;7:309

Sativex, a whole-plant extract made by GW Pharmaceuticals, is categorized as a Nabiximol for evaluation by Evidence-Based Medicine.

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He had a small role in the 1970s 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.

'Evidence-Based Medicine' *continued from previous page*

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, EDIT and the benefits actually provided by cannabis are influenced by patients' expectations that it will be very effective. END 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).[5] 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 and both used a rather harsh synthetic THC-like drug, nabilone, developed by Eli Lilly in the 1970s.

In contrast, a previous comprehensive review[6] found 39 studies that merited inclusion in their meta-analysis (11 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,[8] 30 mg of Marinol (!) was given to two brothers for 14 nights. Its effect on sleep was "poorly understood," the authors concluded.

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Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Nausea and vomiting due to chemotherapy	3 (102)	Dronabinol (2), Nabiximols (1)	Placebo	Nausea and vomiting Complete response	OR (95% CI), 3.82 (1.55 to 9.42)	CBM	0	Low
HIV/AIDS	1 (88)	Dronabinol	Placebo	Weight gain No. of patients who gained ≥2 kg within 6 weeks	OR (95% CI), 2.2 (0.68 to 7.27)	CBM	NA	Low
Chronic pain (neuropathic and cancer pain)	8 (1370)	Smoked THC (1), Nabiximols (7)	Placebo	Pain reduction ≥30% NRS or VAS scores Follow-up 2-15 weeks	OR (95% CI), 1.41 (0.99 to 2.00)	CBM	48	Moderate
	6 (948)	Nabiximols (6)	Placebo	Pain NRS scores (0-10) Follow-up 2-14 weeks	WMD (95% CI), −0.46 (−0.80 to −0.11)	CBM	59	Moderate
	3 (613)	Nabiximols (3)	Placebo	Pain Brief Pain Inventory-Short Form scale (0 to 10) Follow-up 3-15 weeks	WMD (95% CI), −0.17 (−0.50 to 0.16)	CBM	0	Moderate
	6 (267)	Nabiximols (5), Nabilone (1)	Placebo	Patient global impression of change Follow-up 3-14 weeks	OR (95% CI), 2.08 (1.21 to 3.58)	CBM	68	Low
	5 (764)	Nabiximols (5)	Placebo	Neuropathic pain Neuropathic Pain Scale (0-100) Follow-up 5-15 weeks	WMD (95% CI), −3.89(−7.32 to −0.47)	CBM	41	Moderate
	3 (573)	Nabiximols (3)	Placebo	Quality of life EQ-5D scale (0 to 100) Follow-up 12-15 weeks	WMD (95% CI), −0.01 (−0.05 to 0.02)	Placebo	0	Moderate
Spasticity due to multiple sclerosis or paraplegia	2 (519)	Nabiximols (2)	Placebo	50% Reduction in spasticity symptoms NRS (0-10) Follow-up 6-14 weeks	OR (95% CI), 1.40 (0.81 to 2.41)	CBM	0	Low
	2 (519)	Nabiximols (2)	Placebo	30% Reduction in spasticity symptoms NRS Follow-up 6-14 weeks	OR (95% CI), 1.64 (0.95 to 2.83)	CBM	44	Low
	5 (1244)	Nabiximols (4), THC/CBD (1), Dronabinol (1)	Placebo	Spasticity Ashworth Spasticity Scale Follow-up 3-15 weeks	WMD (95% CI), −0.11 (−0.23 to 0.02) −0.32 (−1.58 to 0.95) −0.94 (−2.37 to 0.49)	CBM	0	Moderate
	3 (698)	Nabiximols (2), Nabilone (1)	Placebo	Spasticity NRS or VAS scores	WMD (95% CI), −0.76 (−1.38 to −0.14)	CBM	73	Low
	4 (1433)	Nabilone (2), Dronabinol (1), THC/CBD (1)	Placebo	ADLs Barthel Index of ADL	WMD (95% CI), −0.58 (−1.73 to 0.56) 0.23 (−0.13 to 0.59) −0.03 (−0.39 to 0.33)	Placebo	0	Moderate
	2 (497)	Nabiximols (2)	Placebo	Walking speed as assessed by timing	WMD (95% CI), −0.86 (−3.08 to 1.36)	CBM	24	Moderate
	3 (461)	Nabiximols	Placebo	Global Impression Patient global impression of change	OR (95% CI), 1.44 (1.07 to 1.94)	CBM	0	Low
Depression	1 (66)	Nabiximols	Placebo	Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks	Mean difference (95% CI), 0.15 (−1.0 to 1.31)	Placebo	NA	Very low
	1 (182)	Nabiximols	Placebo	Depression assessed using the Montgomery-Åsberg Depression Scale (0-54) Follow-up 9 weeks	Mean difference (95% CI), 1.90 (−0.22 to 4.02)	Placebo	NA	Very low
	1 (160)	Nabiximols	Placebo	Depression Beck Depression Inventory Scale (0-63) Follow-up 6 weeks	Mean difference (95% CI), 0.69 (−0.76 to 2.14)	Placebo	NA	Very low
Anxiety disorder	1 (24)	Cannabidiol	Placebo	Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes	Mean difference, −16.52 P value = .01	CBM	NA	Very low
Sleep disorder	1 (22)	Nabilone	Placebo	Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks	Mean difference, −19.64 P value = .02	CBM	NA	Low
	8 (539) In other indications	Nabiximols (7), THC/CBD (1)	Placebo	Sleep quality NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.58 (−0.87 to −0.29)	CBM	33	Very low
	3 (1637) In other indications	Nabiximols (3)	Placebo	Sleep disturbance NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.26 (−0.52 to 0.00)	CBM	64	Very low
Psychosis	1 (35)	Cannabidiol	Amisulpride	Mental health Brief Psychiatric Rating Scale Follow-up 4 weeks	Mean difference (95% CI), −0.10 (−9.20 to 8.90)	CBM	NA	Low
	1 (35)	Cannabidiol	Amisulpride	Mood Positive and Negative Syndrome Scale (30-210) Follow-up 4 weeks	Mean difference (95% CI), 1 (−12.60 to 14.60)	Amisulpride	NA	Low
Tourette syndrome	1 (17)	THC capsules	Placebo	Tic severity Shapiro Tourette Syndrome Severity Scale (0-6) Follow-up 6 weeks	Mean difference, −0.70 P value = .03	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette syndrome symptom list (tic rating) Follow-up 6 weeks	Mean difference, −16.2 P value < .05	THC	NA	Low
	1 (18)	THC capsules	Placebo	Tic severity Yale Global Tic Severity Scale (0-100) Follow-up 6 weeks	Mean difference, −12.03 P value = .061	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette Syndrome Clinical Global Impression Scale (0-6) Follow-up 6 weeks	Mean difference, −0.57 P value = .008	THC	NA	Low

Studies included in the meta-analysis by Whiting et al in JAMA are summarized with outcomes and resulting rating of quality 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.

'Evidence-Based Medicine' *continued from previous page*

Overall, the comprehensive review[6] 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[2,6] 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 drowsinessand 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 examples 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 antitumor effect, how do I use it?" The answer to that question is simply unknown. *(Joe D. Goldstrich, 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.[8]

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.[9] 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.

Nevertheless, 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 it past the exclusion criteria, even if the JAMA meta-analysis had 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 blocks to legitimate cannabis research must be removed so good RCTs can be done.

EBM's standards are goals for clinical researchers who are objectively examining medical benefits of cannabis to strive for.

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 consistent results can be expected.

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.

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As Foreseen by McCue

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 reguarly 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.

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 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 by McCue in the accompanying article, the meta-analysis by Whiting et al evidently influenced and limited the discussion. The clinical indications for cannabis use 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."

* Cannabis and Cannabinoids. JAMA 2016:316:2424-5.