

Evidence-Based Medicine: Panacea or Problem?

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Introduction:

I first learned about evidence-based medicine (EBM) during my family practice residency in the late 1990's. I was introduced to it by my mentor, Dr Robert Ewart, who in addition to being a family physician for a number of years, also had a masters in epidemiology. Because of this he was both the smartest and the most obnoxious of the professors in our residency program. He kept insisting on knowing the type and level of evidence of everything we did, and this helped to mold me into the family physician I became. Using the firm foundation of EBM, I practiced family medicine for a number of years in the small town of Quincy Washington, doing full-spectrum medicine including clinic, ER, inpatient, extended care, home visits, obstetrics (for a few years) as well as being chief of staff at the local hospital for about 1/3 of the years I worked there. During the the first thirteen years of practice, evidence based medicine helped me to become the best physician that I could be, ever guiding my path towards best practices and being everything that medicine is supposed to stand for.

And then it failed me.

Evidence-Based Medicine (EBM):

So what is evidence-based medicine, and how could it possibly fail physicians?

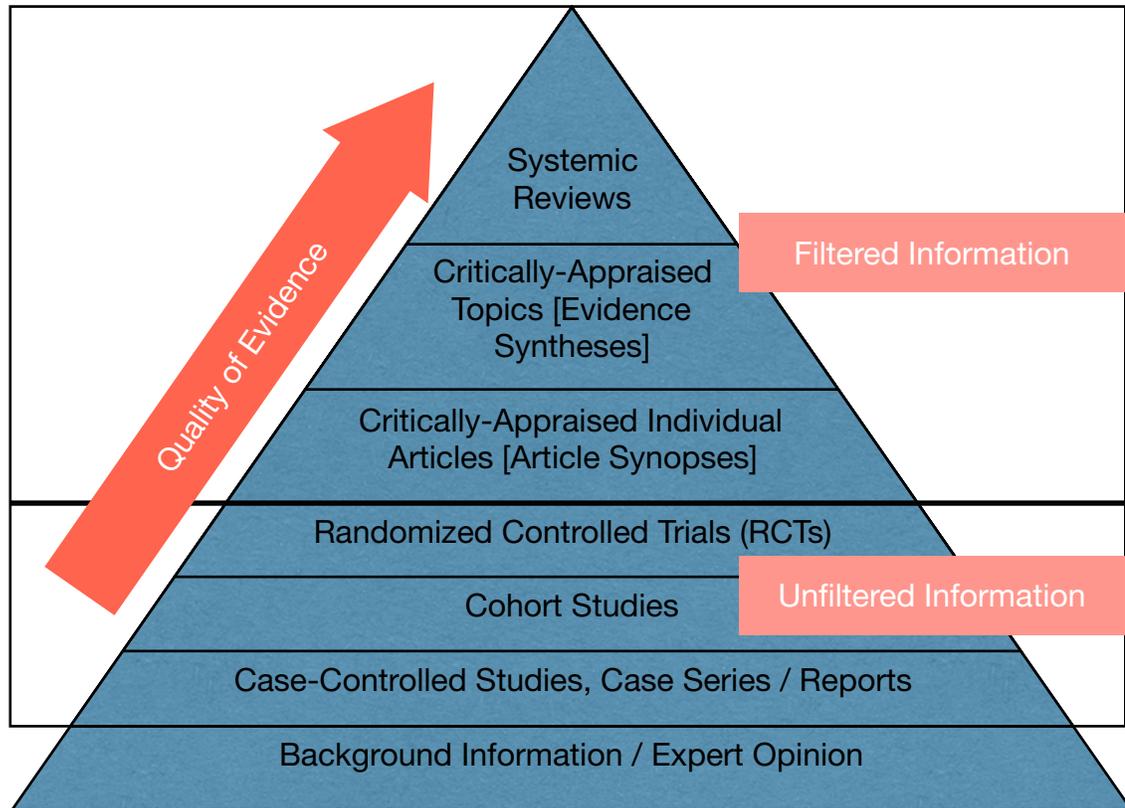
Medicine has always been based on evidence of some sort, although it wasn't until the last century that the scientific method has been truly been applied to medicine¹. Throughout the mid and later 1900's it became more and more apparent that much of what we do in medicine has very little convincing evidence that it works. The term "evidence-based" was first used by David M. Eddy in the late 1980's, with the first paper being published in the Journal of the American Medical Association in 1990 talking about population-level policies². After that it was used as an approach to help teach medical students and residents to treat individual patients. Since then it has come to describe "an approach to decision-making that is used at virtually every level of health care as well as other fields,"³ with the Oxford definition being "medical practice or care that emphasizes the practical application of the findings of the best available current research."⁴

One of the main principles behind evidence-based medicine is that the strongest forms of evidence (meta-analyses, systematic reviews, prospective randomized controlled trials) can lead to strong recommendations regarding therapies, while weaker types of evidence (case-control studies, case reports) can lead to only weak recommendations. Because of this the trend tends to rely more and more on the stronger forms of evidence and less and less on the weaker ones.

As you can see from Figure 1⁵, the strongest levels of evidence are from reviews of all the different available studies on a particular topic, with lower levels being actual studies with the

lowest acceptable data being from case reports. Fortunately they place expert opinion at the bottom (since this can change and isn't necessarily based on any actual data).

Figure 1: Levels of evidence in EBM



Interestingly, the way to get the strongest level of evidence is to not actually do the research yourself, but look into the research out there and do statistical analyses trying to merge the data from several other studies to make, essentially, a study of studies. Only half way up are the ladder are the actual placebo controlled studies that the higher levels of evidence rely upon. Near the bottom of the pyramid are the case reports and case series which the people doing the randomized control trials (RCTs) use to determine what to study next. It is a brilliant, well thought out approach that gives the best and most accurate data that we can possibly get at any moment, and is designed to “keep up with the times” as our current level of knowledge progresses.

So how did this brilliant, modern and excellent system fail me?

My Story:

In 2012 I had a patient with severe knee pain who needed a knee replacement but just couldn't afford it (\$35,000 at the nearby hospital and \$17,000 cash up front 2 1/2 hours away). I had heard from a friend who claimed he was significantly better after some crazy doctor in Idaho injected ozone in his knees. Having run out of options and deciding there was nothing to lose my patient and I drove 11 hours each way for him to get the procedure. I watched him receive the injections and my interest was piqued so I took the course a couple of weeks later. I

figured the class would be rather basic, but was amazed to find that it was quite well researched - the first 1/3 of the course was raw biochemistry! I realized that if it was half as good as they purported it to be it was better than anything else I had seen and bought an ozone machine right there on the spot. My "regular" clinic didn't allow me to do the injections there so I started a clinic in the local nursing home on my weekly day off where I performed the injections and got results every bit as good as advertised.

Evidence-based medicine had failed me by not having the best treatments "rise to the top." Ozone therapy, despite having been around for over 100 years, was still essentially unheard of in mainstream medicine.

I didn't know it at the time, but this course on ozone started me on a journey that has led down all sorts of paths trying to find the best treatments out there. In addition to continuing practicing "regular medicine" in various emergency rooms, I worked at three different alternative medicine clinics, went to naturopathy school, and spent countless hours studying multiple different therapies that are outside of mainstream modern medicine. Recent events with my daughter having seizures likely brought on by mold exposure led me to my latest research efforts into the diagnosis and treatment of mold toxicity using the treatment protocols of Dr Ritchie Shoemaker. These protocols are, despite Dr Shoemaker's heroic efforts to make them mainstream, still far from being standard curriculum in medical schools or residency programs.

What I have found is that if you stick to only the treatments that are generally accepted by academic and mainstream medicine, the results you get with patients will be the same results that everybody else gets. In other words, the standard of care by definition can give no better than standard results, whether or not they use fancy terminology like "best practice." If you look around and research options that may not typically fall under the auspices of having the highest levels of evidence as elucidated by EBM, you may have the opportunity to achieve far better than just "typical" results.

Before going further I have to state that as a physician I fall squarely in the "clinical" rather than "research" category. For me, everything is about getting the best results I possibly can with the patient right in front of me. I am trying to heal man, not mankind. To paraphrase Star Trek, to me "the needs of the one outweigh the needs of the many."⁶ Because of this I have little desire to do placebo controlled studies because I want ALL not just half of my patients to get benefit. In saying this I am in no way minimizing or belittling those in the research arm of medicine. I find them vital to elucidating which therapies work (and possibly why) and moving the field of medicine forward.

Problems with EBM:

So what are the problems with evidence-based medicine? First off, I have to say that it is my belief that the problems with EBM all fall within the "law of unintended consequences." In trying to set up a system that rigorously tries to make sure we have the most scientifically sound information, we could possibly be discarding or at least marginalizing therapies that have tremendous benefit - a proverbial "throwing out the baby with the bathwater."

Following are some of my concerns with EBM (in no particular order):

Randomized Controlled Trials (RCT's): When you do research studies, you want to get the best quality of data that you possibly can. This is done through prospective double-blinded placebo controlled studies. This means that you set up the trial in advance to have it so that roughly half of the patients get the treatment while the other

half get placebo, with neither the researcher or the patients knowing which one they got. This helps weed out any potential bias that can creep into the data. While this gives the most accurate results, these studies are typically very expensive to run - often in the millions of dollars. Because of this, the only people who can afford to do them are either pharmaceutical companies, research universities or the government.

As would be expected, the pharmaceutical companies (and often the research universities) are trying to research something patentable, so they can receive a return on their investment. Why spend millions of dollars researching a vitamin someone can get from the local health food store made by someone else selling it for a fraction of the cost it would take to recoup your investment? Research universities are constantly under pressure to get grants from either businesses or government, and their professors are under the pressure of “publish or perish.” The government (for example the National Institute of Health (NIH)), while potentially somewhat better, has limited resources to be able to study the vast numbers of potentially helpful treatments.

Even with everything being 100% above board, researchers of course want to put the best possible spin on their data (who wouldn't?), so they run the data through all sorts of statistical measures to come up with the analysis that puts their data in the best light.

Because of this, the conspiratorial side of me has to question more the results of the bigger studies with significant funding behind it than some smaller, less well designed studies with little financial or other incentive to fudge the data.

Fraud: Because of the cost involved, there is a financial incentive to make sure that the data you produce gives you the result you want. Who wants to spend \$2 billion on bringing a drug to market if it doesn't get to market? Of note, in an article in the British Medical Journal, one in eight UK scientists admitted to having witnessed research fraud⁷. It appears that the rates of frank fraud, while still low, have risen by almost 10-fold between 1976 and 2007⁸, with fraud being the number one cause of retractions (about 43% of them).

Publishing Bias: Journals prefer to publish studies with positive results (meaning that the treatment showed a difference) rather than negative ones (the treatment showed no difference). Because of this, if you had 19 studies with negative results (no difference) and one study with positive results (made a difference), guess which one will be published? Usually it will be the one that made a difference. After all, as humans we generally prefer knowing what works over what doesn't work.

Also, since there's no requirement to publish a study, someone could, in theory, run the same study 20 times and then pick the one study that gave positive results (given the 5% probability a negative study will have a “p value” (probability value) of ≤ 0.05). They could withhold the other studies and only present that one for publication. Does this really happen? Probably not this blatantly, but it is conceivable that they may do two or three studies and just publish the one with the best looking results.

The Tomato Effect: Another part of publishing bias is the “*Tomato Effect*.”⁹ This was described in an article in 1984 in the Journal of the American Medical Association (JAMA), in which highly efficacious treatments are ignored by publishers and mainstream medicine. Potential causes could be anything from a conflict of interest (medical societies and journals are heavily funded by pharmaceutical companies), discordance with the current medical understanding¹⁰, or simply dismissing it out of

hand while ignoring the data. Historical examples abound: willow bark, vitamin C, exercise¹¹, etc. Very likely Dr Shoemaker's protocols fall in this category.

Peer Review: A subset the Tomato Effect is the problem with peer review. Medical articles are typically reviewed by peer physicians before publication. If the peers don't like or agree with an article it doesn't get published. But the peers doing the reviewing are typically people at the top of the medical totem pole, entrenched in current medical dogma and with every incentive to keep things the way they are. As the famous physicist Max Planck said: "A scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it."¹² Assuming this is true, to some regards it doesn't matter how fast science progresses, the practice of medicine can only progress at a maximally defined rate, determined in part by the length of tenure of the people at the top.

Journal Prestige: The more prestigious the journal the more difficult it can be to get something published in it. Journals like the Journal for the American Medical Association (JAMA), the New England Journal of Medicine (NEJM) and the British Medical Journal (BMJ) are well renowned for their high quality journal articles, and the articles published therein carry significant weight. Articles in other more obscure journals, for instance the African Journal of Infectious Diseases (AJID), could potentially carry an article that could revolutionize modern medicine, but nobody would ever know about it because the journal is practically unheard of in the western hemisphere.

Reproducibility: According to an article by John P. A. Ioannidis, more than half of the medical literature is wrong¹³. This is partly due to the reasons mentioned above, but mostly due to problems with reproducibility. According to him, reproducibility is more important than the results of the original article itself. Sure, it's not as sexy, but because of multiple problems with most studies confirmation of findings is vital. Unfortunately, confirmation or refutation articles are more difficult to get published than new findings.

Systematic Reviews: The highest level of evidence in EBM is Systematic Reviews. Assuming that everything is completely above board, the people doing the reviews are only able to evaluate published studies, and they usually get them only from PubMed. If the original data that they use has the kind of problems mentioned above, that could easily skew the results significantly. The old phrase "garbage in, garbage out" is very true here.

For instance, if someone does a relatively small study on the efficacy of vitamin X in the treatment of disease Y, and gets results that are far superior to standard therapy but the people publishing journal articles refuse to publish it because the results don't make sense to them, then the article never makes it to PubMed. While the people doing the reviews have, in my experience, done a great job of evaluating the evidence out there, they can only evaluate the evidence available to them.

Sample Size: Generally speaking, the larger the sample size (or number of patients participating in the trial) the better the quality of the study. While this is absolutely true, part of me is a little suspicious of very large sample sizes - why? Because if a study needs a very large sample size (very large expense), then the purported benefit is probably very small. For instance, if a treatment is going to make a difference in 80% of the population as compared with 30% of the placebo group, you would be able to get quite good data from a small group of less than 100 people, and not need 10,000

participants to show the benefit. At some point, the large patient populations only run up the cost without adding that much to the data.

Because of this, I suspect that for the most part studies with large patient populations may show a benefit from a treatment, but it (almost by definition) is not a very big benefit (hence the need for the large population).

A notable exception to this is when a very large study is stopped early, due to larger than expected results (positive or negative) that make continued funding of the study either not worthwhile or dangerous (for example if the treatment arm did *significantly* better or worse than the placebo arm).

Patient Population: There are several potential confounding issues with patient populations. Putting racial differences aside, patients in more upscale cash-based practices may well respond differently to the same treatments than do patients in inner city community health based clinics. Differences in living conditions, diet, compliance and co-morbidities can make a big difference with respect to how well a patient does with a particular treatment.

Subject Roles: Also, subject roles can make a big difference with results. Patients enrolled in a study can fall into one of several roles. Subject roles include the *good subject* (tries to corroborate the hypothesis), *negativistic subject* (tries to refute the hypothesis), *apprehensive subject* (tries to place themselves in a favorable light regardless of the results) and *faithful subject* (follows instructions). Double blinding patients can help, but if patients try to guess what is being studied and then place themselves in one of the roles, it can make a big difference in the outcome of the study, especially in studies in the behavioral sciences.

Risk: It is my belief that at least part of the purpose of EBM is to prevent providers from making the mistake of doing treatments that have no benefit (or possibly cause harm), and having people come back and look down on us for doing so. While there is a risk to this, it is my opinion that the risk is far greater that we ignore treatments that are beneficial for the many reasons noted above. I would rather try something that doesn't work than not try something that does work just because the powers that be haven't given it their blessing yet. Of course this is only assuming the treatment is highly unlikely to cause harm in the first place.

Recommendations:

While I don't want to "throw out the baby with the bathwater," I also don't want to throw out the whole bath itself. The concept of evidence-based medicine is a good one, I just feel that while advocating its virtues we need to be aware of its limitations.

For providers (and patients for that matter) it's important to continually research options for treating diseases and medical conditions, and to be open to new ideas without dismissing them out of hand just because they don't have massively expensive studies behind them. Look at the studies and claims that are out there, and judge them with an open mind. Very often they will make claims that sound too good to be true. While that may usually be the case, if the data looks better than anything else out there, and if the treatment is benign (remember, first do no harm), I believe it's reasonable and ethical to try the treatment and see what kind of results you get. Don't be too quick to judge a treatment because the underlying hypotheses don't fall neatly under your background and training.

Whenever you see recommendations by various medical organizations and “best practices”, try seeing them as what they are, recommendations given by a particular establishment which has been approved by the bureaucracy of that establishment as well as those who fund it. This is in no way to say they are wrong - they are usually right and the treatments they espouse are absolutely the “latest and greatest” that the higher levels of EBM can provide at the current time. Just be aware that they are unlikely to contain much of the lesser studied options. Practice in line with the recommendations, but feel free to go above and beyond them if you have other options that in your research and personal experience are even better.

When a patient comes to you with a treatment that you haven’t heard of, don’t dismiss it out of hand and say something like “there’s no evidence for that” without studying the actual evidence. Very often they will be absolutely right. After all, they have all day every day to study their own personal condition. They could very well be more up to date than you are.

If you don’t know something, admit it to the patient, and tell them directly whether you will study more on this or not. If you say you will, look further than Wikipedia or your professional organization’s thoughts on it. Find out what proponents of a treatment say before dismissing it. Very often you won’t understand the background but don’t assume it’s necessarily wrong just because you don’t understand it.

Don’t dismiss a therapy because you disagree with the theory behind it, but dismiss it based on results. In coming up with explanations for how various treatments work, it is entirely probable that the initial explanations aren’t entirely accurate. The question is not so much “why does it work” but “how well does it work?”

In using evidence, don’t be overly dogmatic about the level of evidence - be willing to accept things from less rigorous studies as long as the potential results significantly outweigh the benefit you are getting from current treatments. Absolutely follow the evidence, including the evidence you get when you try some of these therapies on your patients.

Remember the quote by Isaac Azimov, “The most exciting phrase to hear in science, the one that heralds new discoveries, is not ‘Eureka!’ but ‘That’s funny...’”¹⁴. Always watch for unexpected results (good or bad) in any treatment you give your patients. Who knows, your next “that’s funny” may one day revolutionize medicine.

Above all, remember that medicine has historically been an art and only relatively recently has become a science. While the science end is good and important, following it exclusively can turn you into a technician rather than a physician. The best doctors use the latest science, but also establish a caring rapport with their patients - the kind that all by itself can have a healing benefit. This is the part of very-old-school medicine that is sorely missed in today’s managed health care world.

Conclusion:

As the dean of my medical school told us on the first day of med school “in the next 4 years we are going to try to cram as much information in your heads as we possibly can, but I have to warn you that half of what we are going to teach you is wrong. The trouble is that we don’t know which half.” At the time I thought that was crazy, but now, 30 years later, I can truly see the wisdom in these words.

Remember that in finishing a residency or training program you know just enough to (hopefully) not cause too much damage and are able to help people to the level of the average practitioner

in that specialty. Keep studying. Be above average. I am constantly learning new ways of looking at patients and diseases and treatment options, and it is often my patients who bring new things to my attention. Many of my best treatments I learned from patients.

The recommendations above are unlikely to be followed by the majority of the “9 to 5” physicians - those who do the job to get a paycheck. They are also unlikely to be adhered to by many entrenched in the academic arm of medicine. Nevertheless it is my personal experience that practicing medicine “outside the box” is far more rewarding than it ever was using standard techniques. In the words of Robert Frost, “two roads diverged in a wood, and I – I took the one less traveled by, and that made all the difference.”¹⁵

It is my hope that as many practitioners as possible will be willing to look “outside the box” enough to be able to practice a form of evidence-based medicine that makes the “standard of care” substandard.

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