Has evidence-based medicine left quackery behind?

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POINT OF VIEW: **Has evidence-based medicine left quackery behind?**

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Abstract

Evidence-Based Medicine (EBM) is generally considered as the most complete paradigm in the practice of clinical medicine. Its application should preclude all kinds of quackery. Therapeutic reformers of the second half of the 20th century have convinced the medical community that the double-blind randomized controlled trial (RCT) versus placebo is the gold standard in clinical research to establish evidence of treatment usefulness. Nevertheless, this paradigm ignores the importance of non-specific effects in the healing process and can generate misrepresentations. Additionally, because of methodological limitations, RCTs as they are used in practice can give rise to new forms of quackery by promoting drugs that are not useful for the patients who actually receive them, or are so expensive that their value is open to criticism. This is precisely the case when surrogate outcomes, with questionable clinical significance, are used. These can divert attention from clinically relevant outcomes, such as safety issues that are probably the core of treatment evaluation.

The boundaries between quackery and EBM that clinicians are faced with are not so clear-cut. There is a need for doctors to acknowledge their share in quackery and to be continually conscious of the possible pitfalls of their therapeutic practice.

Keywords :

Evidence based medicine; Quackery ; Clinical research ; Randomised Controlled Trials ; Epistemology

The success of complementary or alternative medicines in managing pain, insomnia, depression, anxiety, and indeed many physical complaints, irritates many healthcare professionals. Treatments such as relaxation techniques, chiropractic, therapeutic massage, special diets, megavitamins, acupuncture, naturopathy, homeopathy, hypnosis and psychoanalysis are often considered as "pseudoscience" or "quackery" with no credible or respectable place in medicine, because in evaluation they have not been shown to "work" [1-2].

While psychoanalysis might be decried as a therapeutic technique, faced with a split of this sort between practice and belief, an analyst would say that there must be a defence mechanism at play here and that one explanation is that the supporters of Evidence-Based Medicine (EBM) are denying the role of quackery within their own ranks to maintain a socially acceptable image.

The role of science is to debunk the healing theories of quacks

In 1784, a "placebo" was used for the first time in a medical experiment to debunk the claims by Mesmer that he could bring about cures through "animal magnetism", a new "fluid" he said he had discovered. After a series of "placebo"-controlled experiments, it was concluded that "this fluid has no existence" and that any beneficial effects were due to "imagination" [3]. The use of a placebo became standard in experimental procedures to assess specific effects of health interventions. It enabled science to distinguish "true" (= belonging to medicine) from "false" (= belonging to quackery) hypotheses.

In the same perspective, EBM is generally considered as the most complete paradigm in the practice of clinical medicine, which "de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making, and stresses the examination of evidence from clinical research" [4]. More particularly, therapeutic reformers of the second half of the 20th century have convinced the medical

community that the double-blind randomized controlled trial (RCT) versus placebo is the gold standard in clinical research to establish evidence of treatment usefulness. In this paradigm, the efficacy of an intervention is expressed as a statistically significant difference between two groups, active and placebo, *ceteris paribus.* The non-specific effects, controlled for by the use of a placebo, are considered as experimental noise.

Evidence-Based Quackery?

These "placebo" responses are viewed as a statistical artefact. This contrasts with the rigorous experiments on placebo that emphasize the importance of non-specific effects in the healing process, and shed new light on the ritual of the therapeutic act based on the patient-physician relationship. The therapeutic act can, in some circumstances, be as powerful as the action of a pharmacological agent [5] as shown for example in patients with asthma [6]. This type of placebo effect involves the formation of expectations and appears to have some neural basis [7]. From this point of view, interventions aiming to enhance expectations of reaching a response mediated by a biological effect could be entirely justified. Many bizarre therapeutic rituals based on hypotheses that a patient has "bought into", such as Mesmerism, can bring about unexpected benefits. In this area, patients and doctors rather than "science" define the representations that heal.

The "Quack" in the Doctor

Despite the fact that physicians increasingly use evidence-based treatments, many of the changes observed in clinical practice may not stem from specific effects of these treatments. For example, SSRIs are considered as effective medications for major depressive disorder. Concerning the outcome "response" defined as a reduction of 50 % on a depression rating scale, one meta-analysis estimated a number needed to treat of 7 patients to reach one additional responder as compared with placebo [8]. This is not trivial, but given the classic response rate in placebo-controlled studies on antidepressants (40 %), among antidepressant

responders, 75% (3/4) would have responded to placebo. However, for nearly 100% of responders, physicians and patients believe that the response is an unequivocal benefit of the active treatment.

Even if it is not intentional, in practice EBM involves an element of "quackery" when it relies on misrepresentations of this sort. While the possibility of placebo response is a reason in favour of the need for rigorous randomized controlled trials, in practice it sometimes obscures the translation of treatments efficacy into effectiveness.

EBM is not efficient in detecting hidden quackery

During the 1960s-1970s, when health authorities decided to evaluate the efficacy of new pharmaceuticals with RCTs, they in fact made a surprising choice. It should have been natural for these health authorities to find the appropriate designs and methods to answer the following questions: 1/ has this drug more positive than negative effects? 2/ is this drug of value when it is prescribed by real life physicians for real life patients? and 3/ is the price charged by the firm for the drug compatible with its usefulness? Curiously, RCTs and the statistical tests of hypothesis that conclude them provide no answers to any of these questions. 1/ there is no way to balance positive and negative effects in an objective manner, 2/ the external validity of the results is known often to be very poor and 3/ the economic point of view is often lacking or marginal. This generates new kinds of quackery: drugs approved by EBM but that are not useful for the real patients who receive them, or that are so expensive that their value is open to criticism.

Surrogate outcomes imply surrogate Quackeries

Additionally, in many circumstances, RCT evidence relies on the widespread use of surrogate outcomes. For example, up to 2014, no double-blind RCT has ever shown the efficacy of hypoglycaemic agents (including metformin, insulin and DPP4-inhibitors) for clinically relevant outcome measures (morbi-mortality), among which are microvascular outcomes [9].

HbA1c is a surrogate endpoint that is considered sufficiently reliable to substitute for relevant clinical criteria. However, several randomized trials, with a high level of evidence, disprove the idea that reducing HbA1c is necessarily beneficial for patients [10]. The most striking example is the high global and cardiovascular mortality observed in the group of intensely-treated patients in the ACCORD study [11], even though their HbA1c was 1.1% lower on average than for the controls. In the VADT study [12], with a difference of 1.5% for HbA1c between the two groups throughout follow-up (6.9% vs 8.4%), no difference was observed on overall mortality (FR=1.08; 95% IC 0.83-1.41), cardiovascular mortality (FR=1.22; IC 95% 0.78-1.92), or non-fatal myocardial infarctions (FR= 0.78; 95% IC 0.55-1.11). Yet this does not prevent clinicians from prescribing one or more anti-diabetic agents.

Similarly, while the wide use of pharmacotherapy for adults with alcohol use disorders has been explored by more than a hundred RCTs, there is insufficient direct evidence to determine whether or not treatment with medication leads to improvement in health outcomes (motor vehicle crashes, injuries, quality of life, function, and mortality) [13]. Trials typically focused on consumption outcomes, and the few trials that reported health outcomes were not designed or powered to assess these issues.

There are thus numerous examples of regulatory requirements that are not based on proven benefits in term of public health.

EBM & Safety

Thus, in the area of efficacy, the boundary between quackery and EBM is not always as obvious as is assumed. Moreover, one cannot simply assume, in the short term and under certain conditions in which a treatment has demonstrated apparent efficacy relative to placebo, that it has demonstrated the required cost-benefit balance [14].

In fact, the development of evaluation techniques in medicine has been linked to safety issues [15]. A concern for safety issues is perhaps a better demarcation line between EBM and

quackery than is a focus on efficacy. Indeed, the focus on efficacy in the 1962 amendments to the Food and Drugs Act after thalidomide aimed to improve safety [15].

RCTs became the inescapable gold standard in EBM, with some paradoxical consequences, since they do not function well for safety purposes. Randomisation can induce confounding factors wherever a treatment and an illness can produce similar or fairly similar adverse events (for example death), or if the confounding factor occurs after randomization (this is why blinding is often necessary). RCTs are underpowered to detect adverse events [16] when they are less frequent than the occurrence of the primary outcome. They cannot detect non-specific adverse events. These so-called "nocebo" responses are here again considered as statistical artefacts and are not a matter of concern for EBM. For example it is possible that administering treatments to patients, whether these be active drugs or inert sugar tablets, may have long term harmful consequences by reducing patient perceptions of their own abilities for coping with adversity and for self-cure [14]. Additionally, in the available published evidence from RCTs, safety issues are variably and inconsistently reported [17-18]. The recent contestation of the European Medicines Agency's plans for sharing data from clinical trials by ABBVIE and INTERMUNE [19] illustrates that adverse events of treatments could be considered as "trade secrets" by some of the essential actors involved in EBM.

In other word, EBM can, in practice, sometimes hypnotise doctors into missing safety issues.

Toward a rehabilitation of EBM?

Of course, these critical views aiming to provoke reflection should be nuanced. The definition of EBM set out in this essay, essentially focusing on RCTs versus placebo (because this is the basis for EBM), is a somewhat restricted and possibly misleading definition of EBM. But we suggest that EBM has possibly evolved into something different from what it was originally intended to be. It results rather from the "contamination" of EBM by researchers not addressing the proper questions with appropriate studies, as EBM would, in theory, require.

And indeed, the wrongful use of RCTs for surrogate outcomes, improper comparisons, and doubtful research questions are already widely addressed in the EBM literature. There is moreover a current call for a renaissance of the movement, in the form of "real evidence based medicine", refocusing on a critical examination of the pros and cons of the evidence, which can be combined with context and professional expertise in concrete circumstances. This critical approach contrasts with the vested use of EBM by industry, naïve users, and indeed “true” quacks dressed as EBM experts. Indeed, in this "real" EBM, good patient care would mean that, because we have limited data about a therapy and since we have no data about a particular patient (except maybe his prior exposures), if we are going to treat him scientifically we must accept that this is an experiment, keep a very watchful eye on what happens, and be guided by the data, not by the dictates of some wished-for or internalized model that holds sway simply because it claims to have left Quackery behind.

Conclusion

Of course, distinctions should be made between the EBM paradigm as an ideal [4] and EBM as it is implemented in day-to-day practice, which is, like all human activity, influenced by ideological or economical conflicts of interest [20].

But all in all, boundaries between quackery and the latter type of EBM (the EBM clinicians are dealing with) are far from being clear, and perhaps the distinction is not solely situated where it could be naturally expected (i.e. in the evaluation process).

Possibly the problem lies in the ability of doctors to assume their own share of quackery by not being continually conscious of the possible pitfalls of their therapeutic practice, and the limits of Science as it is implemented.

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