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The Limits and Possibilities of Evidence-based Medicine

Introduction

Evidence-based medicine: what is it? Does such a thing actually exist? Does it have to be spelt out? Is there any other sort of medicine, which isn't based on evidence? And if we speak of proofs, which ones? Is it based on general knowledge, exclusively on scientific knowledge, intuition, feelings or emotions, sure instinct, or something else? On the moods of doctors or consultants, teachers or prophets (*Thus Spake Zarathustra*, etc.), 'voices from above', or could it be weather dependent (for example, an Atlantic depression: atmospheric pressure is so important for health or pain!)? Some Christians would like to have *Bible-based Medicine, BBM*, e.g., the laying on of hands. (see Mark 6, v5; Luke 9, v1; James 5, v14-15; etc…). Or is there a supernatural medicine based on something between 'heaven and earth' and not on evidence? Does this kind of medicine cure, or what does it actually do? Will a tumour completely vanish with this sort of medicine, and do the neurons of multiple sclerosis sufferers recover their myelin sheath?

People nowadays often talk about so-called 'alternative medicine' or 'complementary medicine' (CAM). What is the meaning of this alternative – to conventional/ordinary medicine, consisting of methods like meditation, prayer, deep breathing or, for example, acupuncture, neural therapy, homeopathy or anthroposophic medicine? Is there such a thing as normal, straightforward medicine? **Is there only one, or are there several forms of medicine?** Should we (in that event) dispense with all other forms of medicine? In the Czech Republic we often ask, in cases of doubt, whether the doctor's actions were *lege artis medicinae (*"according the rules of medical art"). In other countries one may well ask if procedures have been carried out *"according to the latest scientific state."*

Over the next few pages we intend to ask these and similar questions and try, at the same time, to consider answers to them.

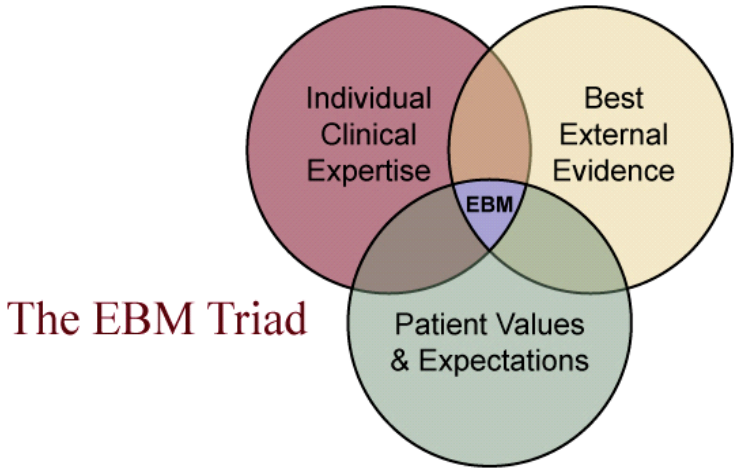
'Evidence-based' medicine

If this term is nowadays used in all grammatical cases (naturally, only in those languages which decline their cases with the nominative, genitive, dative ...), we are talking here about a fairly new concept, which has only been used since the 1990s (a *technical term*). It quickly became a fashionable term, often as part of an uncritical dogma which is not open to discussion. But it is important to discuss and consider it.

Right from the outset we should mention that **so-called evidence-based medicine is to be understood principally in statistical terms**. Its founder is regarded as being the recently deceased Canadian epidemiologist David Sackett (1934-2015). With his colleagues at McMaster University (Ontario, Canada) he formulated the principle of 'evidence-based medicine' – EBM) as the ***"conscious, explicit and critical use of the evidence currently available to make decisions on the treatment of the individual patient"*** (Greenhalgh 2000, p. 17).

In everyday practice this means that it is not sufficient for correct diagnostic and therapeutic procedure to act only in accordance with recognised local experts, (consultants, professors), usual practice, or one's own experiences, but in accordance with the experience of other doctors. Gaining information for practically assessing these experiences is time-limited (as quickly as possible, which means 'online'), and therefore **only possible by using new information technologies** (computers, Internet, etc.). Without these means it is most likely there would not be any EBM. By the way, it is, as an international, statistical, informative concept also certainly a product of current globalisation.

The so-called **EBM triad** formulates the main principles of EBM – illustrated in the diagram below: firstly, there is the personal knowledge and experience of the **doctor**; secondly, the experience of **others**, represented in this case by one of the information databanks (e.g. PubMed, the Web of Science, the Cochrane Library/Database). Finally, the values, wishes, expectations of the **patient**, which are of no less importance, must be included.



The diagram shows us D. Sackett's (1996) famous triad. It represents the intersection between the three propositions we have just mentioned. The definition emphasises its relation to **concrete clinical patients** and not fundamental research or theoretical medicine (anatomy, pathology, pathophysiology, etc.). It had to, and continues to have to contain and provide clear and repeatable proofs.

Sackett was first and foremost a clinical epidemiologist who preferred to work with numbers rather than with living patients (only later did he join a clinical department); this means that he was active primarily in the field of mathematical statistics. For this reason, statistical data and datasets were his strength. Included in this were, of course, randomised studies (based on random selection), random division of intervals, every possible kind of average, correlations, standard deviations and many other statistical measurements which only achieve significance with large numbers.

Sackett was the first in the world, for example, to prove the effects of Aspirin in the prevention of fatal heart attacks and strokes. In his work he also wanted to limit the effects of statistical noise (so-called 'bias') and improve and strengthen the validity of studies. This led to new principles in the design, implementation and interpretation of studies, such as the randomised controlled study, which later became standard methods in all fields. We can't claim that these methods had not also been used earlier – they were, of course, always there, and are part of the basis of all scientific and clinical work. Without them basic research could never function. But it was D. Sackett who, at the right time, formulated the correct idea of making wide-scale use of information technology in research. In this way, his ideas were able to spread all over the world and in all areas of clinical medicine.

As an aside – it was only based on this that it was possible to have medical treatment with protocols or guidelines. However, in this process, the individuality of the patient can easily be lost. Our pioneer was

very aware of this fact. That is why, in the triad shown above, the individuality of the patient is one of the three pillars of EBM – perhaps even the most important one. In any event, it is vital. But one must also admit that this principle of individuality has, in recent times, gradually receded into the background. It's as though the individual were sometimes a hindrance to the statistics involving large numbers; as though the patient wasn't really ill, or didn't fit in with the latest medical descriptions in the textbooks or with the experiences of other doctors, in short, with medicine based on evidence.

Evidence

One must also be aware, with this method, that the evidence described in published articles has its own hierarchy of importance. In case of doubt, we must allocate higher importance to those methods which are higher in the hierarchy. This looks like this (classes of evidence):

1. **Meta analyses** (analysis of the analyses) or systematic reviews
2. **Randomised studies with a control group** (randomised controlled trials) – Intervention studies based on random selection and a control group which is not treated by the test method. Today, probably the most common method.
3. **Cohort trials** – an analytical study, in which one follows a group/cohort over a longer period of time (years and more) and tests a secure characteristic (e.g. morbidity, mortality) in connection with a drug, a treatment method, etc.
4. **Case-controlled studies, controlled clinical trials** – an analytical study. A particular disease is investigated (in the university hospital, clinical centre, etc.) by using a small group (individual cases).
5. **Cross-section studies, case studies** – in this empirical study there is a one-off investigation into a phenomenon at a particular time (content analysis, interviews – mostly in the fields of psychiatry, psychology, sociology).
6. **Case studies/clinical experience** (case reports) – very popular: "Listen to this, dear colleague, what an extremely interesting case I solved in my department just last week!" ("I'm so good!" is often the subtext.) Analytical experience/research, often more about individual validity than general conclusions.
7. **Intervention** in a pathological or pathophysiological process that, hitherto, was not fully known or clear, sometimes on the 'spur of the moment' and difficult to repeat.

What I find very interesting in this is the fact that the so-called double-blinded study is no longer found in the classes of evidence (see the hierarchy above). This is where neither the treating doctor nor the patient know which one is the 'genuine' pill, and which one the 'placebo'; only the researcher knows. I think this is totally right, for in some areas of medicine it is simply not possible to carry out this study, and even if it is possible, then only with skewed results. Let's take as an example acupuncture (or indeed other areas of medicine?). In every case the stimuli of acupuncture points stimulate the dendrites of the first neuron (through needle puncture, laser, electrical stimulation, and others), as also, by the way, do stimuli at other points (= 'non acupuncture points', what is termed sham-acupuncture vs. real acupuncture). Yet, further in the brainstem and in the higher brain structures acupuncture points form something like a complex 'crown' in the projection, association and commissural tracts and are targeted at the other structures which the simple intervention does not reach. Therefore, a whole 'shower' or cascade of impulses spreads out from the acupuncture point, whereas only individual stimuli spread out from the other places.

As has been said, the greatest strength of the EBM method is a high degree of repeatability. Individuality is blurred. This was bound to raise objections. I think that, particularly with the third pillar (the individuality of the patient), Sackett intended to avoid these objections which he naturally heard from his opponents. **You simply cannot reduce the uniqueness of the individual to a merely statistical entity.**

EBM seeks an optimal procedure both in diagnostics and in therapy, with the aid of large numbers and statistical methods. It analyses and evaluates statistically. To achieve a correct result it has also to check the datasets of other similar illnesses and patients, present their characteristics, test the hypotheses, and establish a level of relevance, inter alia. Thus it works with probability variables (theory of probability), i.e. with stochastic modelling.

For some patients, then, the very procedure is offered that has been successfully tried and tested previously with 95% or 99% of patients with similar conditions worldwide (the associated hypotheses are tested to the probability rate of 95% or 99%). If we embark on the same treatment that has already shown itself to be effective in 95% of similarly ill patients, our patient has a good chance of being cured. The statistical success rate is quite high, which does not necessarily correlate with real success in the case of the actual clinical patient. On the other hand, if the doctor does not act sensitively (with feeling, intuitively), the whole individuality of the patient can be lost.

A further problem arises if our patient is not part of the 95%. This will be as many as 50 patients out of 1000. It's equally bad if the odds are not 95%, but let's say a mere 30%. Which medicine do we use now? Medicine that is not evidence based? ...

'Ars medicinae' (The doctor's art)

If we omit the experience of the doctor and the individuality of the patient from the EBM triad (two of the three pillars), patients would be able to treat themselves, particularly in today's world of the Internet. In any event, EBM tends to lend itself to this.

I think many of us, as doctors, have had this experience. A patient goes to the doctor, takes a sheaf of papers from his bag and says – "Doctor, I don't know if you're aware of all this, but I found these articles on the Internet …can you read them?" The doctor then has to explain to the patient all the things that are on the Internet and what they all mean, and only after that can he begin his examination. The patient probably thinks he has found the *'best current evidence'* available on the Internet and brought it along with him (i.e. in the sense of EBM); it might even be that it is better than what the (stupid) doctor has available. **Information from the Internet provides people with many opportunities**. But I'm afraid it does not replace the knowledge and art of medical practitioners (in the sense of acting within the '*lege artis medicinae'*). Yet for patients, especially for the young, who have continual access to the Internet or social networks (Facebook, Twitter, Instagram) and work with them (also on the bus, on the underground, outside in nature, etc.), it is a completely new experience where they seem to be real partners of the doctor, on an equal footing. There is no objection to this, but as we well know, appearances can deceive.

By the way, something similar existed in the past. Around 150 years ago, the so-called 'family doctor books' began to be published, in a way to facilitate self-treatment, and medicine gradually stopped being a domain of the chosen few. Three Englishmen continually maintained that they were suffering from every ailment described in the 'Family Doctor Book' with one exception– puerperal fever. This classic story is called *Three Men in a Boat: To Say Nothing of the Dog* and was written by the Englishman Jerome K Jerome (1889). As well as typical English humour, we find here a lot to think about. I commend it to you.

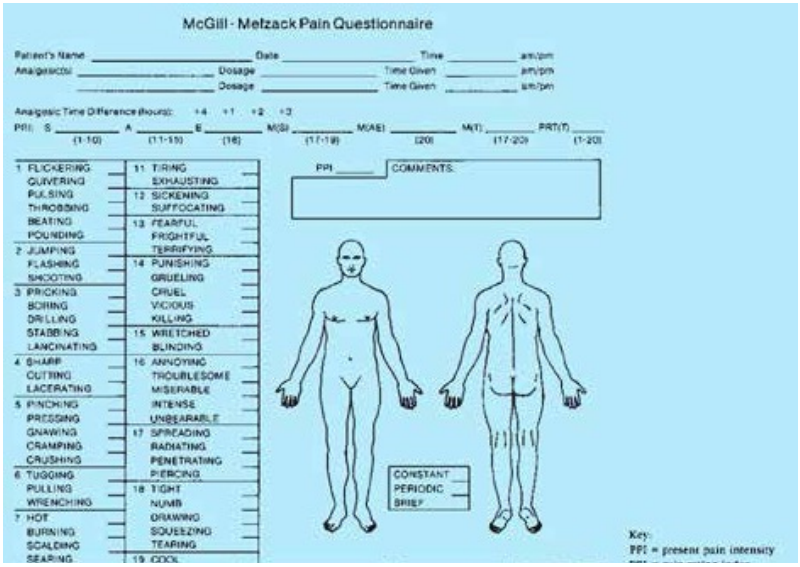
So, are we to treat our patients completely individually or according to Sackett´s EBM method, or something from both 'medicines'? Is it even possible to put the question in this way? I don't think the two possibilities, 'individually' or 'statistically', are mutually exclusive. On the contrary: one should take the best from both approaches for the benefit of the patient.

Let's approach this problem now from a different perspective. Let's take as an example the **treatment of pain**. We're talking here about one of the most common forms of treatment worldwide. The use of pain killers is increasing dramatically. There's no doubt that treatment is pretty successful in practically all fields of pain medicine. The success rate is high, people do not have to suffer pain unnecessarily. The pharmaceutical industry is satisfied and happy. All research in this area is carried out strictly in accordance with EBM. That's clear and understandable.

But what is pain actually? What are we treating with the EBM method when we're fighting pain? The best definition is so vague for the 21st century that it is scarcely credible: ***"Pain is an unpleasant, subjective feeling…"*** says the WHO definition, and some scientists add another clever ingredient to it *"…which every one of us has experienced."* A thought taken from the good old days of the Enlightenment… So pain remains – for better or worse – a great mystery even in the most modern medicine of the 21st century, and resists with every means at its disposal a better, more precise and more objective definition.

We are all very aware of the fact that everyone feels and experiences pain differently. We know how the pathways of the nerves go from bottom to top and back (e.g. hand → brain → hand), but that's all. Even our most modern, scientific medicine with its highly developed technologies cannot measure this feeling objectively. The outcome? Our EBM hasn't a clue with respect to pain. It can't even measure and objectively assess the effect of the most common analgesics (Aspirin, Ibuprofen, Metamizole, Tramadol, etc.). But if Neolithic hunters in prehistoric times chewed the bark of a willow tree to combat pain and fever, or prepared a tincture from it, they were intuitively acting completely correctly, even in the sense of today's EBM, as we now know. (Does 'intuitive' always mean 'unscientific' in today's sense?) For this willow bark contains our Aspirin (acetylsalicylic acid), which has survived over a long period of time and is still today a very modern medicine (although its thrombolytic effects, for example, could only be confirmed by D. Sackett and his EBM method a few years ago).

Pain, still today, depends entirely on the feelings of the patient, and can at most be measured according to a scale, as, for example, with the help of the famous McGill questionnaire (McGill University, Montreal, Canada) – see below. I see a major difficulty when everyone is capable of feeling the same stimulation differently. For example, on the scale of 1-10, one person might say 'one', whereas another says 'five' or even 'ten'. It's no secret that this questionnaire too can only offer a subjective scale. Not to mention the psychological aspect of pain, which has a lot more to do with our brain and our feelings.



McGill pain questionnaire

Our modern medicine is strictly based on objective results and as much as possible avoids all subjective or uncertain opinions or results. But if we don't get any results from the laboratory, x-rays, CT or MRI scans, what then? What do we do with our patient? Our medicine and doctors certainly want to treat the cause of the patient's illness and not merely his symptoms. But what happens if we do not find a cause and therefore cannot *'first make clear the cause'*?

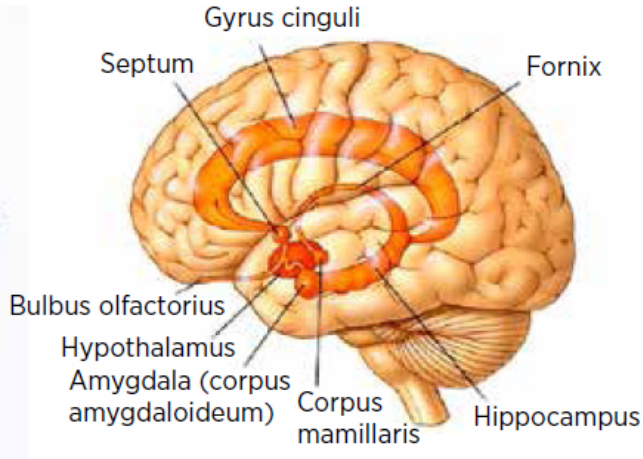
Doctors and patients are then not able to understand each other well, for each can, in the same situation and in the same circumstances, be thinking something different. So their conversation can be limited to the following: "Doctor, today it is a bit better", or "It's about the same," and in a worse case "It

hurts even more." Unfortunately, that is too vague as a quantification. And what's more: the door is wide open for simulation or dissimulation. We experience this every day in our department. When a patient maintains during a consultation that he is suffering from 'unbearable pain', as his doctor I have no chance of verifying his assertion, even though we have done everything possible and then some to alleviate his pain in the last fortnight …

Where does this leave modern, medical science? Are pain and its treatment without precise quantification 'unscientific'? If we formulate the problem in this way, what happens to a significant part of medicine and the pharmaceutical industry?

And now some thoughts on another area : **is there objectively such a thing as love or is it just a matter of human biochemistry**, which is completely impossible to reliably ascertain or prove? If so, then can you somehow treat or cure 'unhappy love'? And how?

Today's biological, scientific medicine teaches us that the emotions are housed within the structures of the brain which we categorise as the limbic system. This lies in the middle part of the brain and surrounds the structure we call the thalamus, although all these structures communicate with each other very intensively with the help of specific neurotransmitters. What we call 'love', is usually accompanied by a heightened activity of the cingulate gyrus and the effects in those areas of the CNS which surround the rear of the limbic system. Some activities in the nearby structures, such as the caudate nucleus, nucleus accumbens, among others (see below) also play a fairly large part in love. So much on the theme of 'love' from the perspective of modern biology.



An objective assessment of love is, however, similar to that of pain– completely impossible to measure precisely, barely possible to assess, and if so, then only subjectively. What can be, for example 'the great love' that everyone would like to experience? Women experience this differently to men. The ancient Greeks had three words for love: Eros, Philia and Agape. But all three terms were only able to describe it as a mere phenomenon or appearance (expression) without knowing precisely what it consists of.

In this respect today's most modern, somatic medicine (including EBM), psychology or psychiatry, is indeed still unclear. Yet every day, doctors see in their consultation rooms patients who are unhappy in love, have damaged or broken relationships, and they then prescribe tablets. What are they? Anxiolytic or sedative benzodiazepines, for example Valium, thymoleptics which lift mood such as tricyclic antidepressants (Imipramine, Amitriptyline), monoamine oxidase inhibitors – MAO and the new SSRIs (selective serotonin reuptake inhibitors) like Fluoxetine (Prozac, Citalopram, etc...), or stimulants such as Amphetamine, which improve and activate patient's motivation or something even better? Are these medicines used strictly in accordance with EBM or instead intuitively, after individual consideration? As I'm not a psychologist or psychiatrist, I'm happy to leave this problem to the experts we have among us,

fortunately, in large numbers; I hope to learn from them the answer to the question as to whether EBM applies in psychiatry too.

Life, sickness and the doctors of the person

If we have already considered these uncomfortable questions – **what, really, is man**? Modern biology offers scant satisfaction in getting closer to this 'essence' of medicine. We learn all sorts of things in school. From those days I still have a quote in my head by the Soviet writer Maxim Gorky (1868-1936): *„Man – how proud does it sound!"* In contrast, the ancient king of Israel, David, who lived about 3,000 years before him (1013-973 BC), experienced the same thing very differently and asked God (rhetorically or with humility and astonishment?): *"What is mankind that you are mindful of them, and human beings that you care for them?"* (Ps. 8, v4.)

The life of every person on earth is limited (fortunately) and this limit is mostly physiological (or pathophysiological). In optimal conditions we can live for a maximum of around 130 years, if we exclude or avoid all negative factors, infections, illnesses, etc. This limit is due to the telomeres (from the Greek 'end of root'), which form the end of our DNA. They are sometimes compared to shoelaces. After every cell division, which is important for the continual renewal of our whole fabric (some physiologists think there are up to 10 million cell divisions every second), they get a bit shorter, which, after millions of divisions, leads to the irreversible demise of our chromosomal DNA. And that means a definite end to life.

And something else for us doctors: **What is life actually?** When does it begin and when does it end? Does it begin at that moment when two gametes join together? Is it at an end at the moment the heart stops beating and the brain begins to be inactive? Or is everything very different from this? Very little is still known about these two areas, more suited to philosophers and theologians than biologists and doctors. For us as doctors, the in-between conditions are the hard nut to crack, for example, patients who have a damaged brain and are in a state of unconsciousness (vegetative state). They cannot speak, they scarcely react at all, only their open eyes stare motionless as though they were staring straight through us. Do they hear us? Are they aware of us? Are they alive or are they just artificially maintained clinical specimens? Sometimes when we hold their hand, stroke it or smile at them, we can get a mute reaction. But is this a conscious response or just a reflex-like reaction? Who knows?

What are we then, we human beings? Just three or four kilos of minerals that remain of us, a little carbon and some water? Or a little more than this? There are still many unanswered questions; there are many difficult issues to resolve. Man is a mortal creature, and the doctor is simply his imperfect companion who may make his life more bearable in some cases, ease his pain and cure curable diseases for a while. Our brain is also far from perfect enough to be able to understand everything, even though we sometimes think it is. Despite all this, it is the human brain, the brain of the creature, that still cannot grasp many things (e.g. immortality, the origin of the universe, time, with its beginning and ending, etc.).

Though we as doctors do everything we can to keep people free of pain and healthy, death waits for us at the end. In the meantime, we should and must make efforts to help the sick as far as is within our power. Where appropriate, with evidence-based medicine, but always also with heart and feeling. **Evidence based medicine is, therefore, not a new or even better form of medicine. It is simply a good, but imperfect method** used by the imperfect human brain; in many cases it can benefit the patient. But it's not a magic formula!

Medicine of the Person is also not a magic formula, but a modus operandi for medicine and doctors which, in my opinion, goes further and gives or offers more, or at least can offer more, also in those cases where EBM is unsuccessful or even fails and breaks down.

Thank you for your kind attention. I hope that this will have given you something to reflect on and that you will have fruitful discussions on this topic in your small groups.