Towards Personalised Theories of Evidence

David Merry, Christoph Schickhardt, Eva C. Winkler

In this paper, we build on arguments that EBM wrongly offers a one-size-fits-all system for assessing evidence in medicine. We focus on a class of conditions we will call 'singular conditions'. Singular conditions encompass rare conditions, as well as those in which causes, prognoses and responses to treatment vary considerably from one patient to another. We argue that the superiority of clinical trials to mechanistic reasoning is considerably lesser in singular conditions. In doing so we build on and generalise Mona Gupta's criticisms of the use of EBM in psychiatry, as well as concerns about the applicability of EBM in the treatment of rare diseases and in personalised medicine.

Our first step is to reinforce Gupta's argument from prognostic variation about the limitations of clinical trials in psychiatry, and to show how this argument generalises to other singular conditions. We argue that designers of clinical trials for singular conditions face a dilemma: the first option is to gloss over patient variation, as in many studies of psychotherapy and arguably the SHIVA trial of genetically targeted cancer treatments. With such study designs on varied populations, the support a clinical trial provides for the treatment of a particular patient is considerably lessened. This problem becomes more serious as the scope for adapting a treatment to a particular patient increases. Alternatively, designers of clinical trials may try to collect homogenous groups of patients. Because of difficulties in recruiting patients, such studies are unlikely to be widely replicated. Furthermore, because of low sample sizes, evidence of side effects will be limited, a problem shared with mechanistic cases in favour of treatments. Thus, the strength of evidence from clinical trials is lesser in singular conditions than elsewhere.

Our second step is to review the case for limiting the use of mechanistic reasoning in EBM, especially the arguments of Howick and Andersen. We argue that insufficient care has been taken in differentiating two different sets of concern: establishing safety, and establishing efficacy.

The best argument against the use of mechanistic reasoning for establishing efficacy, that is, whether an intervention is likely to reduce the symptoms of a disease, is that our understanding of mechanisms in medicine is usually incomplete, making predictions of how they will react under intervention uncertain. Although this is a reasonable point to make generally, scientific understanding of mechanisms within the human body varies. For this reason, we would expect mechanistic reasoning to be stronger in some areas of medicine than in others. Furthermore, we would expect it generally to improve with time.

The argument against the use of mechanistic argument for establishing safety, that is, whether an intervention is likely to cause unwanted side-effects, is more generally applicable, as predicting safety will often depend on understanding a much wider range of mechanisms in the body than predicting effectiveness. Nevertheless, safety concerns vary depending on the kind of intervention. The side-effects of a new drug are harder to predict than those of a minor surgery or lifestyle change. In off-label uses of drugs, evidence about side-effects is already available. The extent to which clinical trials are needed to establish safety will thus vary depending on the kind of intervention in question, and evidence guidelines need to be adapted accordingly.