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"Living is easy with eyes closed . . ." on blinded RCTs and specific and non-specific effects of complex therapeutic interventions☆

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Abstract

Introduction: It is assumed that, as measured during randomised placebo-controlled trials, specific and non-specific effects of an intervention do not interact with each other, and are simultaneously observable. It is argued this assumption means the results of RCTs (particularly for complex interventions, such as homoeopathy) are treated too simplistically.

Purpose of study: To examine if a complex intervention's specific effects and non-specific effects are complementary (in a sense derived and generalised from quantum theory), i.e., correlated sets of observables from an RCT, in which both are necessary to achieve a more complete understanding of the efficacy of an intervention.

Methods: Building on earlier work, and based on the properties of Abelian and non-Abelian algebras, a mathematical argument is developed, which is used to examine the nature of the relationship between a complex intervention's specific effects and non-specific effects as observables from RCTs.

Results: The mathematical argument suggests that it is essentially incorrect to assume specific effects and non-specific effects of a complex intervention (as measured during an RCT of a complex intervention) can be separated into simultaneously measurable, non-interacting sets of observables.

Conclusion: This calls into question not only the legitimacy of conclusions drawn from RCTs, but also the blinded observational stance of the RCT protocol (which currently justifies – and is justified by – a reductionist approach to the efficacy of complex therapeutic interventions). Indeed, such RCTs might well be demonstrating a Heisenberg-type uncertainty between the specific effects of the intervention and the non-specific effects of the consultation, as complementary observable parts making up a whole irreducible phenomenon: the therapeutic process.

Keywords: Evidence-based medicine; RCTs; Specific and non-specific effects; Complex interventions; Abelian and non-Abelian algebras; Quantum theory

Introduction

Evidence-based medicine and randomised placebo-controlled trials. As initially formulated evidence-based medicine (EBM) was "... an approach to health care that promotes the collection, interpretation, and integration of ... patient-reported, clinician-observed, and research-derived evidence (from randomised placebo-controlled trials – RCTs – author's emphasis).[1] The best available evidence, moderated by patient circumstances and preferences, is applied to improve the quality of clinical judgments" [1]. In other words, RCTs were envisaged as just one component of an evidence 'package', whose totality was to be derived from multiple sources [2].

Systematic reviews and meta-analyses of RCTs generally are now taken to represent the 'gold-standard' by which therapeutic interventions–conventional medical and complementary and alternative (CAM) – are judged scientifically acceptable. Other

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[1] Placebo-controlled studies test for specific effects, while comparative effectiveness trials do not try to isolate specific effects.

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forms of evidence and clinical decision-making tend to be either downgraded or ignored; a state of affairs criticised by Cartwright and Rawlins [3–6] who have pointed out the limitations of the RCT. Indeed, as Greenhalgh et al. point out, though EBM has had many benefits, it has also had some negative unintended consequences. While questioning whether the EBM movement is in crisis, they suggest it could be improved if EBM refocused on providing useable evidence that can be combined with context and professional clinical expertise so that individual patients get optimal treatment [7]. More trenchant responses have been elicited from clinicians, not only for EBM's overbearing attitude towards clinical decision-making [8], and perceived intolerance of 'therapeutic pluralism' [9] but also its underlying logical inconsistency [10].

EBM's effect has been to devalue (and in some cases ridicule [11]) interventions or procedures that do not lend themselves readily to the strictures of the RCT protocol (e.g., CAM therapies such as acupuncture, psychotherapy, physiotherapy, and homoeopathy). This, in turn, has led to questioning of the RCT protocol (e.g., by CAM practitioners) and how, in complex interventions [12], it might itself be a source of interference in the therapeutic process [13–15]. As the RCT is now perceived as the principal means by which an intervention's causal effects may be identified, it is important to ensure the RCT protocol is understood in greater depth so that optimal interpretation of its results may be achieved.

Because of the extreme attenuation of its remedies, homoeopathy has the added problem [16] of accounting for observed beneficial effects in trials [17,18] from within the currently accepted reductionist biomedical paradigm of drug action. For example, Brien et al. [19], reporting a 5-armed RCT of homoeopathy in the treatment of active relatively stable rheumatoid arthritis, concluded the positive benefits they found were due solely to contextual non-specific effects of the homoeopathy consultation; not to the specific effects of any individualised single or complex homoeopathic remedies (interestingly, others have pointed out that RCTs designed to observe the specific effects of homoeopathic remedies, say little about the non-specific effects of the consultation when the remedies are non-individualised, or report the disruption to the therapeutic process when the remedies are individualised [12,13]).

Complementarity in biomedicine? In coming to this conclusion, Brien et al. follow the general assumption that specific and non-specific effects of an intervention are separate observables of the RCT protocol, and as such, are considered not to interact or interfere with each other [20]. Here, we examine a different interpretation of the relationship between specific and non-specific effects of an intervention: that far from being separate and non-interacting, specific effects (SE) and non-specific effects (NSE) of complex interventions such as homoeopathy, as observed via the RCT protocol, may be complementary and incompatible with each other in a sense derived and generalised from quantum theory [21]. Such a quantum-like complementarity would mean that in studying the effects of the consultation, it might be difficult to observe simultaneously the pharmacological effects of the medications with the same degree of accuracy. On the other hand, if one were to concentrate on studying the pharmacological effects of medications, it might prove difficult to observe simultaneously the effects of the consultation with the same precision. Yet though incompatible, both sets of observations would be necessary in order to obtain a fuller description of the therapeutic process than either taken alone.

Complementarity is not unusual in biomedicine, e.g., in the sequence of normal pharmacological testing. First, pharmacological effects of medications are studied in phase I–III clinical trials, and only during phase IV trials can the general effects of normal practice be observed in post-marketing surveillance studies. Often the results appear incompatible; the case of antidepressants being a good example.

Thus, in normal practice, antidepressants (such as Prozac, aka Fluoxetine) have been regarded as effective medications [22]. Although their 'side effects' now cause concern (e.g., suicidal tendencies [23,24]), they have earned pharmaceutical companies large profits. However, except for severely depressed patients, the efficacy of antidepressants has been shown to be clinically insignificant against placebo [25]. In the case of severely depressed patients, their putative efficacy is thought to be due more to decreased responsiveness to placebo, than increased responsiveness to the antidepressant medication (Indeed, the pharmaceutical industry has expressed major concerns over the strength of placebo effects versus verum that has bedevilled clinical research into new antidepressants [26]. In addition, it has also been demonstrated in an RCT on the treatment of irritable bowel syndrome, that even when participants knew they were receiving placebo pills, they still got better [27]).

The example of antidepressants above highlights another kind of complementarity in the biomedical field: that of various methods that cannot be applied at the same time and need to be taken in sequence, the sequence being important. Thus (a) if a medication/procedure is studied first in clinical practice (e.g., because it has existed for a long time, such as many CAM complex interventions [28]), then the NSEs (in this case 'side-effects') in general practice are known from experience, and placebo-controlled RCTs are performed to determine the SEs. This is a completely different epistemological situation to (b) when a completely new medication is tested for SEs in RCTs and then only later on are its NSEs (i.e., 'side-effects') observed in general clinical practice. In the two situations (a) and (b), knowledge and outcome are completely different. A case in point here is the Cox2 inhibitors, e.g., Vioxx, which though efficacious were not broadly acceptable because of side effects brought to light in large observational studies [29]. Hence RCTs and observational studies may be considered complementary, and indeed, can complement each other.

Consequently, given what has already been said, if SEs and NSEs (as defined by the RCT protocol) were indeed complementary, then it would be necessary to reassess the meaning of the results of RCTs, particularly those performed on complex interventions. The purpose of this present paper therefore is to provide an argument for the complementarity of SEs and NSEs, and to examine its consequences for how the effectiveness of therapeutic procedures (particularly complex interventions such as homoeopathy) should be adjudged.