sonal anecdotes, with a curiously Australian emphasis, suggesting an immuno-modulatory role for naltrexone in MND. A few further clicks of the mouse and the naltrexone ordering site with costings appeared. Patients with incurable diseases commonly seek “alternative” treatments at great personal financial cost, calculated at thousands of dollars per patient with MND. Often there is insufficient, or, as with naltrexone, no evidence that these treatments are effective. Most patients with MND will consider alternative therapy, irrespective of their educational background or understanding of disease pathophysiology. How each physician approaches the use of complementary and alternative therapies by their patients may develop into an important issue in the therapeutic relationship. Certainly, being aware of the possibility may prove critical. In the patient described by Henderson and McCombe, an unfortunate outcome of irreversible liver failure in a patient with NMD was averted through conventional monitoring of liver function.


Allocation concealment and blinding: when ignorance is bliss

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TO THE EDITOR: Forder et al conveyed that trials without allocation concealment have the potential to mislead. However, it is not true in any meaningful sense that “Without exception, allocation concealment is achievable in all randomised clinical trials. In contrast, it is not always possible to blind people to study treatments received.” Rather, “Masking may be defined as either the process (researchers not revealing treatment codes until the database is locked) or the result (complete ignorance of all trial participants as to which patients received which treatments). A masking claim indicates only the former. . . If masking is possible only some of the time, then clearly reference is being made to the result, and not the process. To be fair, then, one would have to ask if the result of allocation concealment is always possible. . . only the process of allocation concealment, but not its result, can be ensured.”

Forder et al also state that certain methods (including sealed envelopes) are considered to be adequate concealment methods. Sadly, this is true, but only if the emphasis is on the word “considered”, because sealed envelopes are both imperfect at preventing direct observation of future allocations and useless at preventing the prediction of future allocations, even without direct observation. Because the extent of prediction depends on the specific restrictions used on the randomisation, allocation concealment is not even a binary phenomenon, and so to truly assess allocation concealment in a given trial, one must ask how much prediction is possible in that trial.

Allocation concealment is perfect if no observation or prediction is possible, and only partially effective if some prediction is possible. Many trials use randomised blocks, and smaller block sizes tend to allow for substantial prediction. So, while methods aimed only at preventing the direct observations of future allocations may be considered to be adequate, it is clear that in reality they are not.

That the authors failed to use this opportunity to set the record straight indicates their implicit agreement with the incorrect statement that methods aimed only at preventing the direct observations of future allocations are not only considered adequate, but actually are adequate. Pretending that allocation concealment is binary, and hence that it suffices to use methods aimed only at preventing the direct observations of future allocations, represents ignorance that may be bliss, but certainly is not harmless.

4 Berger VW. Quantifying the magnitude of baseline covariate imbalances resulting from selection bias in randomized clinical trials (with discussion). Biomet J 2005; 47: 119-139.

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recent meta-analysis of 55 placebo-controlled trials found that regular vitamin C supplementation had no effect on the incidence of colds in the general population (relative risk [RR], 0.98; 95% CI, 0.95–1.00), but reduced the incidence of colds in people exposed to substantial physical or cold stress (RR, 0.50; 95% CI, 0.38–0.66). Also, regular vitamin C intake reduced the duration of colds in adults by 8% (95% CI, 3%–13%) and in children by 13.5% (95% CI, 5%–21%). Although further studies are needed to evaluate the practical significance of these findings, it is evident that the interpretation by Karlowsky and colleagues that the effect of vitamin C on the common cold may be explained by the break in the double blind is false and should not be reiterated.


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IN REPLY: Allocation concealment refers to ignorance of future treatment assignment before randomisation whereas masking or blinding is most commonly used to refer to the concealment of treatment allocation after randomisation.

There are two criteria for successful concealment of allocation: (i) physical concealment of the process of random assignment to treatment, and (ii) concealment of any pattern of consecutive assignments. Successful concealment of the process must prevent unauthorised access to randomisation lists, envelopes or algorithms; the best way is to use a centralised or remote service for randomisation, whereby an independent party other than the clinician or investigator accesses a secure sequence list or a secure computer system to generate the next allocation.† Successful concealment of the pattern of random assignments prevents investigators from predicting a future treatment assignment on the basis of pattern recognition of allocations to date. Identifying a pattern of previous allocations can occur in open-label trials, in which all parties are aware of allocated treatments after randomisation, or if the blinding of patients and investigators has been compromised. The likely success of concealing the allocation process can reasonably be judged by its description in most trial reports (usually found in the Methods section). However, it is usually more difficult to assess the likelihood that investigators could have predicted future allocations.

Unsuccessful concealment of treatment assignment after randomisation (masking or blinding) should be detailed in the trial report. In circumstances where the blinding has been substantially compromised, exploring the results of treatment separately among participants who were unblinded and those who remained blinded, should be considered, although these are no longer randomised comparisons. In the study by Karlowsky et al, the placebo did not match the active treatment in taste, which alerted the investigators to the likely occurrence of significant unbiasing within the study. To their credit, the investigators sought to quantify the extent of unbiasing by means of a questionnaire at study close-out, and reported their findings by results of these responses. The particular grouping of responses, however, has been the subject of some discussion, and while the interpretation of a possible placebo effect has been challenged, it has not necessarily been disproven. (The absence of a placebo effect could be proven only if information concerning perceived benefits of vitamin C related more to cold frequency than cold symptoms. Biologically, it is far more plausible for a placebo effect to result in fewer cold symptoms reported than fewer colds reported.) This trial highlights the impact of compromised blinding in the reporting of trial results, emphasising the importance of maintaining adequate blinding for reliable and unbiased trial results.

Good quality reporting of trials, in accordance with the CONSORT statement, includes describing the processes in enough detail to assure readers that any pattern of randomisation is not predictable. Authors should report issues relating to allocation concealment, blinding (where appropriate) and randomisation sufficiently to convey the message that these essential trial principles were successfully achieved.


Achieving equal standards in medical student education: is a national exit examination the answer?

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TO THE EDITOR: We read with interest the article by Koczvara and colleagues proposing a national exit examination for all Australian medical school graduates. It is refreshing to see interest in educational outcomes, a distinctly different trend from earlier reforms that shifted curricular focus from content to the learning process, exemplified by problem-based learning (PBL). Although the early process-focused programs were based on sound pedagogy current at their time, their educational outcomes have been relatively disappointing, with marginal or no demonstrable improvements in knowledge structures, clinical skills, or generic capabilities such as self-direction. Rather than an indictment of PBL, the results may reflect what was missing in those programs: explicit focus on educational outcomes, alignment of assessments with outcomes, and attention to the learning environment.

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