and has a pecuniary interest in protecting the copyrights, reputation, quality and further development of these surveys.

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Clinical trials of drug and behaviour therapies: methodological issues

Shimazu *et al*[1] designed a randomised controlled trial highlighting the efficacy of family psychoeducation compared with treatment as usual in the maintenance treatment of major depression. By definition, the index trial was a pragmatic trial. The authors did not use behavioural 'placebo' control groups, although in such a trial they are not necessarily needed. However, this study has faced bias with regard to recruitment and selection procedures, such as the exclusion of previous non-responders. Sample homogeneity is one of the ways to enhance the power of the study. The authors excluded patients who received electroconvulsive therapy, which improved the homogeneity. The bipolarity status, number of previous episodes, duration of untreated psychosis (DUP) and associated specifier (e.g. melancholic, atypical and psychotic features) might have been taken as inclusion criteria to improve it further. Alternatively, as clinical relevance is the primary consideration in pragmatic trials, differences in treatment structure (e.g. number of antidepressants, doses and length of treatment/follow-up sessions) may be ignored if they reflect clinical practice.

Participants might have a preference for only antidepressant or combined therapy, and this preference might undermine adherence (which is not addressed in this study), influence drop-out rate, and even affect treatment response.[2] This could be avoided with a two-level randomisation design: first, randomised to two different treatment protocols; and second, randomised to receive preferred treatment. The participants' expectation, which might be a confounding factor, was not a concern in this trial.

The frequently raised question 'Does combining family psychoeducation therapy with antidepressant treatment enhance the maintenance of treatment effects following drug withdrawal?' can only be addressed following drug withdrawal.[3]

Allegiance effects could have been minimised if the drug and family psychoeducation were each administered by professionals who did not have primary allegiance to the type of therapy they were administering and expertise in its administration. This issue is not addressed clearly by Shimazu *et al*.[1]

In this pragmatic trial, the goal was to duplicate clinical practice, including practitioners' clinical judgements in tailoring treatments to patients. However, therapy protocols need to be clearly specified (especially whether receiving antidepressant or antipsychotic drugs) and fidelity to treatment protocols maintained if a clearly defined therapy is to be evaluated and the therapy is to be duplicated by others. Information obtained from this drug–behaviour therapy trial might be maximised if measures of the putative therapeutic mechanisms of behavioural treatment (e.g. self-efficacy, symptoms-related coping) were obtained.

Adherence data can provide useful information about treatment acceptability in pragmatic trials. Adherence appears to be more easily assessed with drug therapy. Measures of adherence with behaviour therapy are often limited to self-report, although completion of in-therapy tasks and/or homework assignments and tape recorders capable of monitoring the use of relaxation tapes have been used as 'objective' measures of adherence.[4] Had the authors taken some of these measures, the confounding due to adherence would have been reduced.

The authors could have entered some additional factors into the Cox proportional hazards analysis, such as adherence, DUP, type of antidepressant, predominant side-effect and psychotic status of current episode, which may have made the analysis better powered.

The methodological issues we discuss here are not considered immutable, but are expected to evolve as investigators creatively tackle design issues when conducting drug–behaviour trials.

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Authors' reply: Biswas *et al* are correct that our study was a pragmatic trial, but beyond that there seem to be many misunderstandings and we are happy to respond to the points they raise.

First, we did not compare family psychoeducation with treatment as usual (TAU). The comparison was between psychoeducation plus TAU *v.* TAU alone. We asked the pragmatic question whether adding psychoeducation to TAU alone was any better than TAU and were able to answer it positively. The strengths and weaknesses of this type of comparison are fully discussed in our paper.

Second, we did not exclude previous non-responders. We did focus on responders to pharmacotherapy in the index episode because this was a trial of maintenance treatment, and it is very hard for us to logically imagine such a trial without focusing on responders. In addition, it appears meaningless to us that Biswas *et al* would like to assess bipolarity in a trial of major depression.

Third, Biswas *et al* seem to insinuate that we ignored 'differences in treatment structure (e.g. number of antidepressants, doses and length of treatment/follow-up sessions)'. Our Table 1 shows that they were comparable between the two arms, where the doctors in charge of TAU were kept unaware whether their patients had their family participating in family psychoeducation or not. We strictly abided by the principle of ceteris paribus.

Fourth, we agree that adherence and allegiance are important but often ignored aspects in clinical trials. Adherence to the family psychoeducation by the family members was maximised because there was no missed session. Adherence to TAU by the patients may have been optimal or suboptimal but this is not a valid concern in our context because we minimised performance bias (i.e. differential TAU intensity between the two arms) by masking the doctors. Adherence to family psychoeducation by staff was ensured through videotaping and supervision. All these are explained in the paper. On the other hand, we admit we failed

to mention our allegiance to psychoeducation as researchers and therapists. We tried to minimise its influence by masking both the doctors in charge of TAU and the outcome assessors.

Fifth, Biswas *et al* advise that we examine effect modifiers and moderators. In our paper we explain that we did examine one strong empirically supported candidate variable in this regard, namely expressed emotion.[1] And we failed to confirm its role as effect modifier or moderator.

Last but not least, unfortunately we must confess that we do not fully understand how the authors' proposed 'two-level randomisation' or psychoeducation to 'enhance the maintenance of treatment effects following drug withdrawal' might work. We are more than willing to continue this discussion in order to 'creatively tackle design issues when conducting drug–behaviour trials'.

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Understanding the neuroprotective mechanisms of lithium may have clinical significance

The article by Forlenza *et al*[1] is a useful addition to the literature. Disease-modifying drugs for dementia, and in particular Alzheimer's disease, are sorely needed. Despite very strong preclinical science, translational studies have been relatively limited, so this sort of interventional trial is welcome.

The authors highlight the inhibition of glycogen synthase kinase-3 beta (GSK-3B), a serine/threonine kinase involved in the regulation of numerous intracellular signalling pathways, as the likely mechanism for any neuroprotective effects. Although it is true that there is a literature supporting this pathway, other potential disease-modifying pathways are influenced by lithium. For example, up-regulation of autophagy, an intracellular protein degradation pathway which is able to degrade mutant proteins associated with neurodegeneration, can rescue a variety of animal models of neurodegenerative disease.[2] In fact, GSK-3B inhibition inhibits autophagy via its effect on the mTOR (mammalian target of rapamycin) pathway. Despite this, lithium ultimately induces autophagy via a dominant mechanism involving inositol monophsphatase inhibition.[3] These distinctions are not trivial, as understanding the interactions of these pathways allows for more rational treatment design. For example, lithium and rapamycin (a drug which inhibits mTOR) provides greater neuroprotection in fly models of Huntington's disease than either drug alone.[4] Furthermore, numerous US Food and Drug Administration-approved drugs which are autophagy up-regulators have been identified. Many of these may have a more favourable side-effect profile than lithium, and preclinical work suggests their efficacy in animal models of neurodegenerative disease.[5]

The potential mechanisms for neuroprotection by lithium extend well beyond inhibition of GSK-3B. Working out which are most important is of more than scientific interest as it is likely to allow rational drug design and better selection of currently available drugs with neuroprotective potential.

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Authors' reply: We agree with the comments by Dr Underwood reinforcing that the mechanisms by which lithium may exert a neuroprotective effect in patients with amnestic mild cognitive impairment[1] still must be clarified. The inhibition of glycogen synthase kinase-3 (GSK-3B) by lithium is a plausible effect, given its pivotal role in the pathogenesis of Alzheimer's disease, but most likely not the only one. In addition to the prevailing mechanism of action involving the inhibition of inositol monophosphatase and downstream effects towards the up-regulation of autophagy, many other neurobiological effects have been attributed to lithium. These include the inhibition of apoptosis and the up-regulation of neurotrophic cascades.[2] The modification of these intracellular signalling systems by lithium has been shown to yield neurotrophic and/or neuroprotective effects, which have been consistently demonstrated in cell culture and animal models. These effects are probably unspecific and may be beneficial to patients with distinct psychiatric and neurodegenerative diseases, including bipolar disorder,[3] amyotrophic lateral sclerosis[4] and Alzheimer's disease.[1]

We hypothesise that the inhibition of GSK-3B by lithium is more specific to processes that ultimately lead to the formation of neuritic plaques and neurofibrillary tangles. According to the 'GSK3 hypothesis of Alzheimer's disease', overactive GSK-3B accounts for memory impairment, Tau hyperphosphorylation, increased beta-amyloid production and local plaque-associated inflammatory responses mediated by the microglia.[5] The inhibition of GSK-3B is currently regarded as a candidate disease-modifying approach for the treatment and prevention of Alzheimer's disease, and specific inhibitors such as NP-031112 are being tested in phase II clinical trials (www.clinicaltrials.gov). Therefore, lithium may contribute to the attenuation of the pathological process in Alzheimer's disease through inhibition of GSK-3B, and deliver additional, unspecific benefits via modification of other signalling pathways that favour autophagy, preclude apoptosis and up-regulate the secretion of neurotrophic factors in the brain. Presumably, the interplay of complementary mechanisms is necessary to warrant clinically relevant benefits, which we were able to show in our study.[1] We thus speculate that the effects of lithium on multiple homeostatic systems downstream from membrane receptor-based neurotransmission may in fact represent an advantage as a candidate drug for the treatment of complex neurobiological diseases. In our study, the doses of lithium used were very well tolerated. This,