

## Correspondence

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## Dose and effect in CBT for schizophrenia

Many thanks to Jauhar and colleagues for their interesting and thought-provoking review of cognitive-behavioural therapy (CBT) for schizophrenia,<sup>1</sup> and especially for making their data publicly available. Previous discussants (Byrne,<sup>2</sup> McKenna *et al*<sup>3</sup>) have commented on the lack of consideration given to ‘dose’ (i.e. number of sessions) of CBT. The relation between dose and effect is almost a classic in psychotherapy research.<sup>4</sup> It has more recently been shown to be of importance in reviews of other psychosocial therapies (e.g. Gold *et al*<sup>5</sup>). Together with the obvious plausibility of such a relationship, this seems to be enough reason to examine the dose–effect relation carefully. I used the effect sizes calculated by Jauhar *et al* and extracted the number of sessions from the original papers (I was able to do this for 32 of the 52 studies). I then ran a meta-regression (functions *metagen* and *metareg* from R package *meta*) for each of the four outcomes (Fig. 1). Most studies used between 10 and 20 sessions, with a few outliers in both directions. The regression lines show little support for an increase of effect with dose. On the contrary, there are tendencies in the opposite direction for all outcomes. The paradoxical observation is that effects seem to be strongest when

few sessions were provided (significant for positive symptoms,  $P = 0.0005$ ).

Obviously this analysis has a number of limitations.

- (a) As McKenna *et al*<sup>3</sup> noted in their response to the comment by Byrne,<sup>2</sup> participants were not randomised to different doses.
- (b) Dose is likely confounded with duration<sup>6</sup> and may also be confounded with masking and control interventions.<sup>1</sup>
- (c) There may be differences between the scheduled and the received dose, and this was not reported consistently in the original papers.
- (d) Dose data were not independently extracted by two people.

However, I think one can conclude from these analyses that dose is unlikely to have masked a clearer effect in these data. A more detailed re-analysis of this data-set may be warranted. In general, the dosage of psychotherapy should be considered carefully in future studies.

- 1 Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *Br J Psychiatry* 2014; **204**: 20–9.
- 2 Byrne RE. CBT for psychosis: not a ‘quasi-neuroleptic’. *Br J Psychiatry* 2014; **204**: 489.
- 3 McKenna PJ, Radua J, Jauhar S, Laws KR. Authors’ reply. *Br J Psychiatry* 2014; **204**: 490.
- 4 Howard KI, Kopta SM, Krause MS, Orlinsky DE. The dose-effect relationship in psychotherapy. *Am Psychol* 1986; **41**: 159–64.
- 5 Gold C, Solli HP, Krüger V, Lie SA. Dose-response relationship in music therapy for people with serious mental disorders: systematic review and meta-analysis. *Clin Psychol Rev* 2009; **29**: 193–207.
- 6 Gold C. Quantitative psychotherapy outcome research: methodological issues. In *Psychotherapy Research: Foundations, Process, and Outcome* (eds OCG Gelo, A Pritz, B Rieken): 537–58. Springer, 2015.

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**Authors’ reply:** Gold’s findings using the end-of-treatment effect sizes from our meta-analysis of CBT for schizophrenia<sup>1</sup>

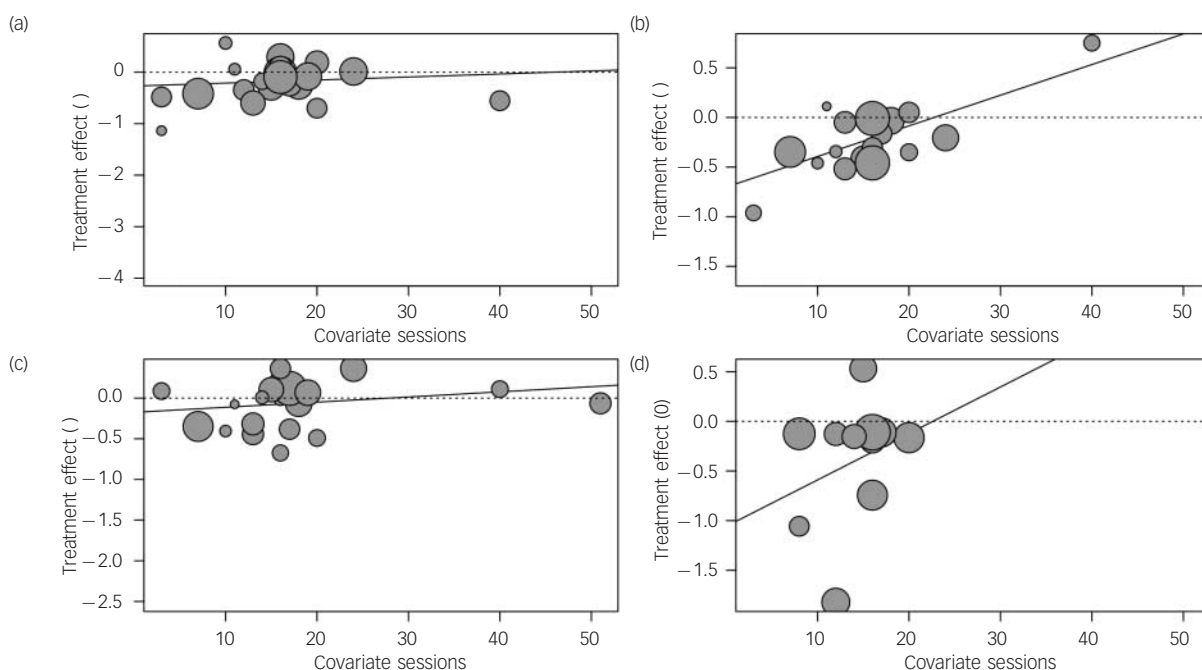


Fig. 1 Meta-regression for (a) total symptoms, (b) positive symptoms, (c) negative symptoms and (d) hallucinations.

(available at [www.cbtinschizophrenia.com](http://www.cbtinschizophrenia.com)) are of interest and may have implications for clinical practice. In particular, the National Institute for Health and Care Excellence's<sup>2</sup> (NICE) current recommendations that at least 16 sessions of therapy should be provided now seem open to question. As noted by Taylor & Perera<sup>3</sup> in their recent editorial in the *BJPsych*, this view is not evidence-based; instead it appears to derive from an impression gained by the Guideline Development Group that 'the evidence for CBT is primarily driven by studies that included at least 16 planned sessions' (NICE,<sup>2</sup> p. 240).

Our database might additionally be used to examine two important claims about CBT for schizophrenia that have surfaced in the past year, one that it has more pronounced effects in treatment-resistant patients,<sup>4</sup> and the other that it is most effective when delivered in an individually tailored, formulation-based form.<sup>5</sup> Both these claims are based on meta-analyses that included only quite limited numbers of studies (12 and 13 respectively) and so could benefit from being examined in the full data-set of available studies.

- 1 Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *Br J Psychiatry* 2014; **204**: 20–9.
- 2 National Institute for Health and Care Excellence. *Psychosis and Schizophrenia in Adults: Treatment and Management* (NICE Clinical Guideline CG178). NICE, 2014.
- 3 Taylor M, Perera U. NICE CG178 *Psychosis and Schizophrenia in Adults: Treatment and Management* – an evidence-based guideline? *Br J Psychiatry* 2015; **206**: 357–9.
- 4 Burns AM, Erickson DH, Brenner CA. Cognitive-behavioral therapy for medication-resistant psychosis: a meta-analytic review. *Psychiatr Serv* 2014; **65**: 874–80.
- 5 van der Gaag M, Valmaggia LR, Smit F. The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: a meta-analysis. *Schizophr Res* 2014; **156**: 30–7.

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### Should adherence to antidepressants be judged in isolation in ischaemic heart disease?

We read the article by Krivoy *et al.*<sup>1</sup> addressing an important clinical issue of medication adherence, especially antidepressants in patients with ischaemic heart disease, and its impact on mortality rates. The authors must be congratulated for evaluating the data of such a large sample after controlling for many known covariates. However, there are certain issues which require clarification, before accepting the 1:1 relationship of adherence to antidepressants only and reduced mortality rate.

First, it is unlikely that the patients would be adherent or non-adherent to antidepressants in isolation; hence, it is possible that those who were adherent to antidepressants were also adherent to other medications and this overall adherence to medications led to reduction in mortality rates. As a result, there is a need to provide the data in terms of adherence to other medications and include these as a covariate. Second, with such a large sample size, the authors should have evaluated the effect of each antidepressant or class of antidepressant on mortality. This is important from a clinical practice point of view, because this could have provided information about which antidepressants are more useful. Third, for assessing the confounding effect of comorbidity, the authors used the Charlson comorbidity index, which is considered to be a good predictive marker for mortality.

However, it is important to note that the index does not take dyslipidaemia into account. Accordingly, a covariate which is an important risk factor for mortality in patients with ischaemic heart disease could have been left out. Fourth, certain other covariates that can also influence mortality, for example alcohol use or dependence, were not taken into account. Fifth, although the authors have acknowledged that information on causes of death was not evaluated, it remains an important limitation. Sixth, the authors have not evaluated the prescribed doses in terms of being in the therapeutic range or not. This is important because antidepressants such as amitriptyline and duloxetine are prescribed by physicians at lower doses for indications other than depression or anxiety. Seventh, in the study, about three-quarters of patients were aged 65 years or older, with 38% of the study sample aged more than 74 years. If it is presumed that many of these patients were dependent on others for intake and purchasing of the medication, this should also be evaluated. Last, adherence to antidepressants was assessed in terms of medication possession ratio. In real terms this does not suggest that patients would have taken all the doses which they purchased. It is often a clinical experience that although patients purchase the prescribed medications, they do not take all the purchased medications. Consequently the authors would have overestimated the medication adherence.

- 1 Krivoy A, Balicer RD, Feldman B, Hoshen M, Zalsman G, Weizman A, et al. Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study. *Br J Psychiatry* 2015; **206**: 297–301.

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**Authors' reply:** We thank Grover & Abbas for their thoughtful comments on our paper. Most of the points they raise are appropriate and valid. Unfortunately, analysis of a large database (nationwide scale) has its strengths and limitations, including lack of access to some variables, as they suggested. The findings in our paper are indeed associational and not causative. Therefore, any notion regarding the causal effect of antidepressant adherence on mortality is speculative and validation in a prospective interventional study is required. It is possible that adherence to antidepressant treatment affects survival through moderators that were not examined in our study. Nevertheless, it appears that better adherence to antidepressants in patients with ischaemic heart disease is associated with increased survival rate. It is of note that our measure of adherence is unique in combining data regarding both prescribed and purchased prescriptions (unfortunately we did not have data on actual consumption of the pills). Most of the epidemiological studies on adherence use only purchase data as a measure of adherence. Therefore, we believe that our adherence measure reflects better the level of antidepressant adherence compared with previous similar studies.

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