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, and especially for making their data publicly available. Previous discussants (Byrne, McKenna et al) 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. It has more recently been shown to be of importance in reviews of other psychosocial therapies (e.g. Gold et al). 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 noted in their response to the comment by Byrne, participants were not randomised to different doses.
(b) Dose is likely confounded with duration and may also be confounded with masking and control interventions.
(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.


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doi: 10.1192/bjp.207.3.269

Authors’ reply: Gold’s findings using the end-of-treatment effect sizes from our meta-analysis of CBT for schizophrenia

Fig. 1 Meta-regression for (a) total symptoms, (b) positive symptoms, (c) negative symptoms and (d) hallucinations.
Should adherence to antidepressants be judged in isolation in ischaemic heart disease?

We read the article by Krivoy et al., 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 adherence to antidepressants in isolation in ischaemic heart disease? 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.

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.
Are NICE guidelines losing their impartiality?

I applaud Taylor & Perera1 for their clear discussion of these very important issues. For me the most important sentence in their piece is the last one, that ‘CG178 appears to be open to a critique of bias’. This is not the first occasion that such issues have arisen and I think that it is time for the National Institute for Health and Care Excellence (NICE) to take a long hard look at the relative standards that are set for making recommendations about the use of non-pharmacological and pharmacological treatments. A previous example is seen in CG72 Attention Deficit Hyperactivity Disorder;2 where it would appear that a lower quality of trials was allowed and lower standards of evidence were required to support behavioural approaches than for pharmacological treatments. A similar criticism can be made about CG28 Depression in Children and Young People,3 and there are no doubt others. Although the ultimate recommendations made in these guidelines may, on one level at least, be sensible, I believe that the evaluation and interpretation of the evidence, including the selection of trials and assessment of their quality as well as their outcomes, should be the same regardless of the mode of treatment. If NICE, who as Taylor & Perera point out occupy an extremely important position in our lives, then decide to interpret or weight evidence differently, this should be clear and transparent. NICE must be above all claims of bias and need to work hard to ensure that they regain this position.


Declaration of interest

D.C. has accepted fees and/or research funding from Janssen Cilag, Shire, Lilly, Lundbeck, Novartis, and Viitor in the past 3 years. He receives royalties from Oxford University Press.

Authors’ reply: We thank Professor Coghill for his interest in our editorial, and his positive comments supporting our views. It is notable that, thus far at least, the only comments either of us authors have received have been positive despite our editorial being deliberately tendentious, and what can appear to be a worldwide promotion of cognitive–behavioural therapy for psychosis. A related point is that even if cognitive–behavioural therapy for psychosis was in fact highly efficacious, there seems to be such a dearth of clinical psychologists in the National Health Service that accessing even an initial assessment can take up to 18 weeks – a long time to wait for someone actively psychotic.

Declaration of interest

M.T. was chair of SIGN 131 guideline, and has received fees and/or hospitality from Janssen, Lundbeck, Roche, and Sunovion in the past 3 years.

Hearing voices: are we getting the message?

In a large study of adults with bipolar disorder, Upthegrove and colleagues report associations between childhood sexual abuse and lifetime occurrence of mood congruent auditory and visual hallucinations; however, no associations are seen for delusions or diagnoses of psychotic disorders.1 The findings are similar to a recent study of psychotic symptoms in borderline personality disorder (BPD) that shows high lifetime prevalence of auditory and other hallucinations (with predominantly negative contents) but not delusions.2 Together these studies provide important clues regarding mechanisms of specific psychopathology. They also raise a wider question regarding the relationships between psychotic and common mental symptoms such as mood and anxiety.

Using interviews with the Present State Examination, the BPD study2 found that 80% of 30 patients (collected from a specialist personality disorder service) had experienced psychotic symptoms at some point during their lifetime. Auditory hallucinations were reported by 50% and visual hallucinations were present in about a third of the sample. Although the form of auditory hallucinations was similar to that in schizophrenia, the content was predominantly negative and critical even when they occurred outside an affective episode. Contents of visual and olfactory hallucinations were also mainly negative and unpleasant. Delusions, however, when present, indicated previously undiagnosed psychotic disorder. Although the study did not examine maltreatment specifically, such history is common in BPD. Thus mood dysregulation, which is an important feature of both BPD and bipolar disorder, might explain the emergence of negative, self-critical auditory/visual/other hallucinations in victims of childhood maltreatment.

The findings along with other research indicate psychotic symptoms are common and can occur in the context of non-psychotic disorders. A recent phenomenological study found that auditory hallucinations are present in a diverse sample of people with various diagnoses and clinical histories, where they are associated with fear, anxiety, depression and stress as well as positive or neutral emotions.3 In young people, auditory hallucinations have been reported to occur alongside mild to moderate depression and anxiety, where they are a marker of severity, for example multiple psychiatric comorbidity or suicidality.4 Similarly, a recent study found that depression, anxiety and psychotic symptoms measure a single, common underlying factor in the population, with psychotic items measuring the more severe end of this continuum.5 Together these findings suggest that similar to depression and anxiety, psychotic symptoms – particularly auditory hallucinations – are common mental symptoms. Therefore, psychotic phenomena should be routinely included in epidemiological assessments of psychiatric morbidity. Diagnostic classification systems should acknowledge the presence of psychotic symptoms in non-psychotic disorders to reflect evidence, which will also allay worries among patients and many clinicians who tend to associate hallucinations exclusively with psychosis.

Correspondence

Authors’ reply: We thank Khandaker et al for their response to our paper, and are in broad agreement that psychotic symptoms are more common than currently recognised in mood disorders. Indeed our previous work has highlighted this and likewise the importance of mood symptoms in psychosis.1,2 In our present study the presence of hallucination but not delusion was most frequent in those with a history of child sexual abuse.3 Hallucinations in particular may occur in non-psychotic diagnoses in the presence of childhood or later trauma.4 Thus hallucinations may have less specificity for psychosis than one might expect given the weight positive symptoms have in diagnostic terms.5 Khandaker et al’s proposal that diagnostic systems should acknowledge the presence of these experiences in non-psychotic disorders is important. This recognition would allow clinicians to better accept diagnostic uncertainty, allay worries provoked by an exclusive association of hallucinations with psychosis, and enable further investigation as to underlying causality within a symptom-specific approach.


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doi: 10.1192/bjp.207.3.272a

Childhood non-affective psychoses: data analysis

The epidemiology of psychosis in children is a story of even smaller numbers than for psychosis in grown-ups. But how much smaller? The short report of Tiffin & Kitchen1 on incident cases of schizophrenia in children in 2010–2011 is a well-needed addition to a limited descriptive literature on psychosis in children. I have a couple of points about the analysis, which I feel might clarify the report.

The authors point out at the outset the heuristic that earlier onset cases of a disorder might have a ‘greater loading of causal factors’. This does not seem to be correct – all cases of a given disorder represent the interrelation of a number of risk factors on a causal pathway – it is therefore unclear why earlier cases would represent the culmination of pathways with a greater number of causal factors. The authors may mean that earlier onset psychoses could represent individuals with stronger risk factors for the disorder. However, although this is usually correct for diseases in general, this point rests on the assumption that there is a single underlying outcome under study, which has long been contested.2 Assuming this heterogeneity is related in some way to the clinical heterogeneity of schizophrenia across people of different ages and with different risk factor patterns, this may explain the large number of false positives identified in Tiffin & Kitchen’s study.

Second, although the authors present confidence intervals (presumably based on Poisson standard errors), it is important to point out what the intervals are referring to – this study attempts to capture all cases within a surveillance approach, rather than to sample the target population. In this case, the confidence intervals refer to the underlying randomness of the disease process, rather than to the design of the study.3 Confidence intervals used in this way are not meaningless, but they may not be strictly necessary here – it seems that reporting the crude rate in this type of study is an almost equally informative approach for the purposes of this research. Furthermore, uncertainty about the true rate of the disorder due to random variability (‘error’) in the disease process likely pales in comparison with the systematic error introduced by biases in this design.


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Authors’ reply: To clarify, we did mean to state that earlier onset psychoses could represent individuals with stronger risk factors for the disorder. We agree that there is likely to be some heterogeneity in the outcomes, even if the loading of putative causal factors is similar for any set of given individuals. However, there is evidence that cases of childhood-onset psychosis spectrum disorders in general, when carefully defined, tend to be more severe and more homogeneous, with stronger family histories of schizophrenia spectrum disorders than adult-onset cases.1,3 Therefore, there may still be much to be learned about causality, even if the assumption of homogeneous clinical outcomes does not hold strictly true. Moreover, we believe the high rate of false-positive reports is likely to be due, at least in most instances, to clinicians initially wrongly attributing perceptual disturbance in children to an underlying psychotic illness. In most cases, it is likely that voice experiences and other potentially psychotic phenomena may result from processes that may be conceptualised as more psychologically driven, such as dissociation. Such experiences are commonly reported in community samples of children and adolescents, who are likely to share few, if any, of the risk factors associated with the development of early-onset schizophrenia spectrum disorders.4

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doi: 10.1192/bjp.207.3.272a
We would concur with Dr Bhavsar that the use of confidence intervals (which were indeed based on Poisson standard errors) in this situation may not have been strictly necessary. However, they do attempt to communicate some of the uncertainty regarding the estimates of incidence. We also agree that in this study most of this uncertainty will be due to the degree of completeness of case ascertainment using the surveillance design, rather than variability in the disease process.


2 Hanson DR, Gottesman II. The genetics, if any, of infantile autism and childhood schizophrenia. J Autism Child Schizophr 1976; 6: 209–34.


Correspondence

Effect of duration of psychological therapy on recovery and improvement rates: evidence from UK routine practice. BJP, 207, 115–122. The title of the paper was incorrectly amended by the publisher; no inference of effect was possible from the observational data reported and the paper should have been titled: Duration of psychological therapy: relation to recovery and improvement rates in UK routine practice. Figure 1, p. 117: the reported sample n following age exclusion was 630 too low; a corrected Fig. 1 appears alongside. This affects data reported regarding age exclusion under ‘Selection of patients’ (p. 116), where 385 rather than 1015 were excluded. The online version of this paper has been corrected post-publication, in deviation from print and in accordance with this correction.

doi: 10.1192/bjp.207.3.273

Fig. 1 Selection of patients from the Clinical Outcomes in Routine Evaluation (CORE) database. CORE-OM, CORE Outcome Measure.
Are NICE guidelines losing their impartiality?
Dave Coghill
Access the most recent version at DOI: 10.1192/bjp.207.3.271

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