### NICE guidance on psychological treatments for bipolar disorder: searching for the evidence

**Sameer Jauhar, Peter J McKenna, Keith R Laws**

The recent National Institute for Health and Care Excellence guidelines for bipolar disorder offer a number of recommendations for the psychological treatment of bipolar disorder. Scrutiny of the evidence on which these guidelines are based reveals significant flaws in the methodology and conduct of the relevant meta-analyses, and calls into question the interpretation of the evidence.

The revised National Institute for Health and Care Excellence (NICE) Bipolar Guideline 185 (CG185), published in September, 2014, makes several recommendations about psychological treatments. These cover the acute treatment of people with bipolar depression and the longer-term management of adults in secondary care (there are no recommendations about the psychological management of mania). Specifically, NICE recommends that people with bipolar depression in primary care and adults with bipolar depression in secondary care should be offered, “a psychological intervention that has been developed specifically for bipolar disorder and has a published evidence-based manual describing how it should be delivered, or a high-intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with recommendations in the NICE clinical guideline on depression” (recommendations 8.3.1.1 and 8.3.1.3).

In the longer term, NICE recommends offering “a family intervention to people with bipolar disorder who are living, or in close contact, with their family in line with the NICE clinical guideline on psychosis and schizophrenia in adults” (recommendation 8.3.1.5). These patients should also be offered, “a structured psychological intervention (individual, group or family), which has been designed for bipolar disorder and has a published evidence based manual describing how it should be delivered, to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression” (recommendation 8.3.1.6).

NICE clearly regards psychological interventions as important. The NICE Pathways, an online tool that acts as a quick and easy reference for NICE guidance, positions them as first-line treatment for adults with bipolar disorder who are not in secondary care, and places them on an equal footing with pharmacological treatments in the longer-term management of the disorder. In these circumstances, the evidence on which the recommendations are based and the decisions about how this is interpreted need to be of the highest quality.

**The evidence base**

The NICE recommendations for bipolar disorder are based on a series of meta-analyses that were commissioned from the National Collaborating Centre for Mental Health (NCCMH). Perusing this documentation, the first thing that confronts the reader is how many meta-analyses were done—around 170 meta-analyses of individual psychological interventions. Examined therapies included cognitive behavioural therapy (CBT) and mindfulness-based CBT; psychoeducation and therapy for treatment adherence; and more niche interventions such as dialectical behaviour therapy, social cognition and interaction training, and collaborative care. Outcomes included depressive and manic symptoms (both at post-treatment and at follow-up), relapses (including all relapses and manic and depressive relapses), and a range of social measures. Wherever possible, each therapy was examined both when delivered individually and in a group format, and when compared against treatment as usual and against other active treatments. As a result, each meta-analysis contained only a few trials—the most was 6—and over half consisted of only one trial.

When many analyses are undertaken, some of the findings will inevitably be positive at a significance of 0·05—the criterion that seems to have been adopted by NICE—purely by chance. Bonferroni correction, the classic method for dealing with this statistical problem, is strict and probably not appropriate because many of the measures are related to each other, but a method such as the false discovery rate for non-independent variables could easily be implemented. However, NCCMH did not correct for multiple comparisons in any way.

**The meta-analyses of acute treatment for bipolar depression**

The intervention with the most studies available for meta-analysis was CBT. A meta-analysis of six trials of individual CBT versus treatment as usual gave an effect size in the small range (standardised mean difference [SMD] –0·31) at post-treatment (table). The benefit, however, was not maintained in four trials that included follow-up data. Two meta-analyses of group CBT reported no benefit at post-treatment or follow-up. There were significant findings in two single-trial meta-analyses that compared CBT with an active control (supportive therapy), but in both cases these favoured the control intervention.
The other intervention for which a reasonable amount of information was available was psychoeducation. Two meta-analyses, each containing two trials, reported that online psychoeducation produced no significant symptom reduction compared with treatment as usual, either at post-treatment (SMD −0.18, −0.63 to 0.26) or follow-up (SMD −0.36, −1.09 to 0.37). Group psychoeducation likewise had negative results compared with treatment as usual at post-treatment (SMD 0.14, −0.17 to 0.46, two trials) and follow-up (SMD 0.40, −0.07 to 0.87, one trial).

Family psychoeducation was reported to be beneficial at post-treatment compared with treatment as usual (SMD −0.73, −1.35 to −0.10) and with active control (SMD −0.40, −0.80 to −0.00), but family psychoeducation was not reported as beneficial at 12 months follow-up compared with treatment as usual (SMD −0.15, −0.69 to 0.39), or with active control (SMD −0.10, −0.56 to 0.36); however, all these three meta-analyses contained only one study each.

### The meta-analyses of relapse prevention

In a meta-analysis of four studies, individual CBT was of significant benefit compared with treatment as usual for the outcome “any relapse” (risk ratio (RR) 0.67, 0.53–0.86). However, this meta-analysis did not include a large trial by Scott and colleagues, even though it was included in subsequent meta-analyses examining depressive and manic relapses separately. When this trial, which had negative findings, ie, the overall relapse rates of CBT and treatment as usual were not significantly different at any time, is added to the meta-analysis, the overall result becomes non-significant (RR 0.79, 0.59–1.07) (figure). NCCMH have not responded to a request to provide more information on the decision to exclude this trial (McKenna P), personal communication.

The NCCMH meta-analyses examining the effects of psychoeducation on relapse had inconsistent findings. One meta-analysis, which included three studies of individual psychoeducation versus treatment as usual, recorded no benefit (RR 0.81, 0.64–1.02). However, a meta-analysis of two trials of carer-based psychoeducation versus treatment as usual did find a significant effect (RR 0.61, 0.44–0.86). There were positive effects for psychoeducation in two of three other meta-analyses, but each of these only contained a single trial.

### The composite meta-analyses

One might be forgiven for wondering where, in this maze of contradictory findings, the evidence supporting the NICE recommendations comes from. The answer seems to lie in the fact that NCCMH undertook more than 30 additional meta-analyses that pooled data from different types of psychological intervention. One of these combined online psychoeducation (two studies) and individual CBT (four studies) and reported a small but significant benefit on depressive symptoms compared with treatment as usual at post-treatment (SMD −0.23, −0.53 to −0.08). However, a combined meta-analysis of eight studies involving five group interventions (psychoeducation, mindfulness-based CBT, CBT, social cognition and interaction training, and dialectical behaviour therapy) was negative at end of treatment (SMD −0.24, −0.64 to 0.16). In the same way, the combined relapse-preventing effects of three individual psychological interventions (psychoeducation, therapy for treatment adherence, and CBT) in five studies compared with treatment as usual was found to be significant (RR 0.74, 0.63 to 0.87), but five studies of three group interventions (psychoeducation, CBT, and mindfulness-based cognitive therapy) were not (RR 0.86, 0.61–1.20).

Combining psychological interventions does not, it seems, result in findings that are any less contradictory. Nor is the logic behind this strategy easy to understand, particularly because the interventions that were grouped together were quite different.

### Risk of bias

Nowadays, it is considered essential to take study quality into account when interpreting results from meta-analysis. A clear consensus of opinion suggests
that the different sources of bias, including inadequate randomisation, not blinding outcome evaluations, and failure to control for attrition, should be rated separately, not by means of a single quality score. NCCMH rated various individual aspects of quality for the studies that were included in their meta-analyses, and NICE combined these ratings in a table that summarised the findings of the composite meta-analyses. Almost all the meta-analyses examining outcomes at post-treatment were based on studies that were rated as being of low or very low quality (the only exception was the outcome of hospital admission for collaborative care versus treatment as usual, which received a moderate rating). The same was true at follow-up, where only the composite meta-analysis of individual psychological interventions versus treatment as usual for the outcome of relapse received a moderate rating.

This being so, one might expect to see caveats about any positive findings that emerged. Yet in the section of the NICE guideline “Linking evidence to recommendations”, cautionary notes are conspicuously absent: it is stated only that there is evidence that psychological interventions might improve symptoms and reduce the risk of relapse and hospital admission, “though the evidence for particular psychological interventions varies in quality”. Group interventions, integrated cognitive and interpersonal therapy, and psychoeducation for families are described as showing promising results.

Are NICE’s recommendations for psychological treatments evidence based?

NICE guidelines provide what is in effect a detailed blueprint for good clinical practice. They are not statutory, although making them so has been suggested. Via the NICE quality standards, they will almost certainly affect the decisions health commissioners in the UK make about what services they are going to fund.

In the case of psychological treatment of bipolar disorder, the recommendations seem to go beyond the evidence. It seems probable that many clinicians and researchers would not come to the strong conclusions that NICE did based on frequently negative meta-analytic findings from mostly low-quality studies. Methodological concerns include not incorporating the large well-conducted study by Scott and colleagues in a key meta-analysis, and not taking study quality into consideration. Statistical drawbacks included many meta-analyses being undertaken without correcting for multiple comparisons. Finally, something analogous to the increasingly recognised problem of selective reporting in clinical trials seems to be operating: positive meta-analytic findings are cited approvingly and negative ones are excused or ignored.

What can be done to address this situation? First, doing many meta-analyses is not conducive to interpreting their results. The blunderbuss approach taken by NCCMH needs to be replaced by something more targeted and, one is tempted to say, more conventional. Second, study quality needs be actively incorporated into the presentation of the conclusions. Stating that an intervention is supported by meta-analysis but that most of the included studies are low quality at best gives a mixed message and is at worst a contradiction in terms. Perhaps most importantly, the process whereby NICE converts meta-analytic (or other) findings into recommendations needs to be transparent and appropriately critical.

Contributors

PJM and KRL reviewed the NCCMH documentation and did the modified meta-analysis shown in figure 1. KRL and SJ searched and reviewed other relevant literature and online materials produced by NICE. All three authors jointly wrote the article.

Declaration of interests

We declare no competing interests.

References


