NICE Guidance on psychological treatments for bipolar disorder: searching for the evidence.

The revised National Institute for Health and Care Excellence (NICE) Bipolar Guideline 185 (CG185)\(^1\), which appeared in September 2014, makes a number of 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 recommend 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, adults in secondary care should be offered:

- 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).

and:

- 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 in bipolar disorder. The NICE Pathways, an online tool that acts as a quick and easy reference for NICE guidance (http://pathways.nice.org.uk), positions them as first line treatment for adults 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 relating to how this is interpreted, need to be of the highest quality.

The evidence base
As always with NICE, the above recommendations are based on meta-analysis, in this case a series of meta-analyses that were commissioned from the National Collaborating Centre for Mental Health (NCCMH: available at http://www.nccmh.org.uk/downloads/). Perusing this documentation, the first thing that strikes the reader is the large number of meta-analyses that were conducted – there are around 170 meta-analyses of individual psychological interventions (plus a number of composite ones; see below). These examined therapies ranging from cognitive behavioural therapy (CBT) and mindfulness-based CBT, to psychoeducation and therapy for medication adherence, to niche interventions such as dialectical behaviour therapy, social cognition and interaction training and collaborative care. Outcomes considered included depressive and manic symptoms both at post-treatment and at follow-up, number of relapses, including all relapses and manic and depressive relapses, and also a range of social measures. Where possible, each therapy was separately considered when delivered individually and in a group format, and against treatment as usual (TAU) and other active treatments. As a result, each meta-analysis contained only a small numbers of trials – the largest was 6 – and over half included only one trial.

When many analyses are performed, some of the findings will inevitably be positive at a significance level of 0.05 – the criterion that seems to have been adopted by NICE – purely by chance. Bonferroni correction, the classical method for dealing with this statistical problem, is notoriously strict, but other more appropriate methods exist, for example the false discovery rate (FDR) for non-independent variables\(^2\). However, no correction for multiple comparisons of any type was carried out by NCCMH.
The meta-analyses of acute treatment for bipolar depression

The intervention with the most studies was CBT. As shown in Table 1, a meta-analysis of 6 trials of individual CBT versus TAU gave a significant result in the small range (standardized mean difference [SMD] -0.31) at post-treatment. The benefit, however, was not maintained in 4 trials that included follow-up data. Table 1 also shows that two meta-analyses of group CBT found no benefit at post-treatment or at follow-up. There were significant findings in two single-trial meta-analyses which compared CBT to an active control (supportive therapy), but in both cases these favoured the control intervention.

Table 1. Meta-analyses of symptom reduction in bipolar depression with CBT

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>Number of trials</th>
<th>Effect Size (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual CBT vs TAU</td>
<td>End</td>
<td>-0.31 [-0.53 to -0.08]</td>
</tr>
<tr>
<td>Individual CBT vs TAU</td>
<td>Follow up</td>
<td>-0.19 [-0.46 to +0.08]</td>
</tr>
<tr>
<td>Group CBT vs TAU</td>
<td>End</td>
<td>-0.55 [-1.12 to +0.02]</td>
</tr>
<tr>
<td>Group CBT vs TAU</td>
<td>Follow-up</td>
<td>+0.06 [-0.48 to +0.60]</td>
</tr>
<tr>
<td>Individual CBT vs active control</td>
<td>End</td>
<td>+0.41 [+0.12 to +0.70]</td>
</tr>
<tr>
<td>Individual CBT vs active control</td>
<td>Follow-up</td>
<td>+0.49 [+0.04 to +0.94]</td>
</tr>
</tbody>
</table>

SMD – standardized mean difference

Negative effect sizes indicate that CBT is superior to control; positive effect sizes that CBT is worse than control

The other intervention for which a substantial amount of information was available was psychoeducation. Two meta-analyses, each containing two trials, found no evidence of significant symptom reduction for online psychoeducation compared to TAU, 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 versus TAU at post-treatment (SMD +0.14 [-0.17 to +0.46], 2 trials) and follow-up (SMD +0.40 [-0.07 to +0.87], 1 trial). Family psychoeducation was found to be beneficial compared to TAU and to active control at post-treatment (SMD -0.73 [-1.35 to -0.10] and -0.40 [-0.80 to -0.00], respectively) but not at follow-up (SMD -0.15 [-0.69 to +0.39] and -0.10 [-0.56 to +0.36], respectively); however, these three meta-analyses contained only a single study.
The meta-analyses of relapse prevention

Here there was a significant effect of individual CBT compared to TAU for the outcome ‘any relapse’ in a meta-analysis of 4 studies (risk ratio (RR) 0.67 [0.53 to 0.86]). However, this meta-analysis failed to include a large trial by Scott et al\(^3\), even though it was included in subsequent meta-analyses examining depressive and manic relapses separately. When this trial, which had negative findings, is added to the meta-analysis, the overall result becomes non-significant (RR 0.79 [0.59 to 1.06]) (see Figure 1). (NCCMH have not responded to a request to provide more information on the decision to exclude this trial.)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Relapse / Total</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Ball 2006</td>
<td>0.88</td>
<td>0.54</td>
<td>1.43</td>
</tr>
<tr>
<td>Jones 2013</td>
<td>0.60</td>
<td>0.36</td>
<td>0.99</td>
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<tr>
<td>Lam 2003</td>
<td>0.58</td>
<td>0.41</td>
<td>0.84</td>
</tr>
<tr>
<td>Zaretsky 2008</td>
<td>1.15</td>
<td>0.38</td>
<td>3.55</td>
</tr>
<tr>
<td>Scott 2006*</td>
<td>1.04</td>
<td>0.82</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>0.79</td>
<td>0.59</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Figure 1. The NCCMH meta-analysis of CBT versus TAU for the outcome ‘any relapse’ modified to include the trial by Scott et al\(^3\).

Two other meta-analyses (which both consisted of only one trial) found no benefit on relapse rates for either individual CBT versus active control (RR 1.13 [0.81 to 1.58]) or group CBT versus TAU (RR 1.17 [0.72 to 1.91]).

Meta-analyses examining the effects of psychoeducation on relapse had inconsistent findings. One, that included three studies of individual psychoeducation versus TAU found no benefit (RR 0.81 [0.64 to 1.02]). On the other hand, a meta-analysis of two trials of carer-based psychoeducation versus TAU did find a significant effect (RR 0.61 [0.44 to 0.86]). There were also positive effects for psychoeducation in two out 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 NICE’s recommendations comes from. The answer seems to lie in the fact that NCCMH also carried out a number of further meta-analyses (30+) that pooled data from different types of psychological intervention. One of these combined online psychoeducation (2 studies) and individual CBT (4 studies) and found a small, but significant benefit on depressive symptoms compared to TAU at post-treatment (SMD -0.23 [-0.53 to -0.08]). However, a combined meta-analysis of five group interventions (psychoeducation, mindfulness based CBT, CBT, social cognition and interaction training and dialectical behaviour therapy, 8 studies altogether) 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 medication adherence and CBT, 5 studies altogether) compared to TAU was found to be significant (RR 0.74 [0.63 to 0.87]), but those for three group interventions (psychoeducation, CBT and mindfulness based cognitive therapy, 5 trials altogether) were not (RR 0.86 [0.61 to 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 when 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 also suggests that the different sources of bias, including inadequate randomization, lack of blindness and failure to control for attrition among others, should be rated separately, not by means of a single quality scale. NCCMH rated multiple aspects of quality for all the studies that were included in their meta-analyses, and NICE combined these ratings in a table that summarized the findings of some of the composite meta-analyses (Tables 34 and 35, p.257-8). At post-treatment, almost all the meta-analyses were based on studies that were rated as being of low or very low quality (the only exception was the outcome of hospitalization for collaborative care versus TAU, which received a ‘moderate’ rating). The same was true at follow-up, where only a meta-analysis of individual psychological interventions versus TAU for the outcome of relapse received a ‘moderate’ rating.
This being the case, one might expect there to be caveats about the positive findings that emerged. Yet in the section of the NICE\(^1\) guideline ‘Linking evidence to recommendations’ (p262), cautionary notes are conspicuously absent: it is simply stated that there is evidence that psychological interventions may improve symptoms and reduce the risk of relapse and hospitalisation, ‘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 blueprint for good clinical practice. They are not statutory, although making them so has been suggested\(^6\). Via the NICE quality standards, they will almost certainly influence the decisions health commissioners make about what services they are going to fund.

In the case of psychological treatment of bipolar disorder, the recommendations appear to go beyond the evidence. It seems likely that many clinicians and researchers would not come to the strong conclusions that NICE did based on what were more often than not negative meta-analytic findings from mostly low-quality studies. There are also methodological concerns (failure to include the large well-conducted study by Scott et al\(^3\) in a key meta-analysis, not taking study quality into consideration), as well as statistical issues (carrying out a large number of meta-analyses but not correcting for multiple comparisons). Finally, something analogous to the increasingly recognized problem of selective reporting in clinical trials\(^7\) seems to be operating: positive meta-analytic findings are cited approvingly while negative ones are played down or ignored.

What can be done to remedy this situation? Firstly, carrying out vast numbers of meta-analyses is not conducive to easy interpretation of their results. The blunderbuss approach taken by NCCMH needs to be replaced by something more targeted and, one is tempted to say, conventional. Secondly, study quality needs to be actively incorporated into the presentation of the conclusions – stating that an intervention is supported by meta-analysis but that all the included studies are low quality at best gives a mixed message and is at worst a contradiction in terms. Thirdly, and perhaps most importantly, the whole approach to the
interpretation of meta-analytic findings needs to be more tough-minded and critical; giving any appearance of setting the bar for this too low can only lead to doubts about rigour and impartiality.

References

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