Kendall, Tim and Morriss, Richard K. and Mayo-Wilson, Evan and Meyer, Thomas D. and Jones, Steven H. and Oud, Matthijs and Baker, Mark R. (2016) NICE guidance on psychological treatments for bipolar disorder. The Lancet Psychiatry, 3 (4). pp. 317-320. ISSN 2215-0374

Correspondence

Response to "NICE guidance on psychological treatments for bipolar disorder: searching for the evidence", Personal View, by Sameer Jauhar, Peter J McKenna, Keith R Laws on 4 February 2016

Prof. Tim Kendall, FRCPsych, Director, National Collaborating Centre for Mental Health; Medical Director and Consultant Psychiatrist, Sheffield Health and Social Care NHS Foundation Trust, Sheffield, UK

Prof. Richard Morriss, MD, FRCPsych, Chair of the NICE Bipolar (update) Guideline Development Group; Consultant in General Adult and Community Psychiatry with Nottinghamshire Healthcare NHS Trust; Professor of Psychiatry and Community Mental Health at the University of Nottingham, Nottingham, UK

Dr Evan Mayo-Wilson, MPA, DPhil, Assistant Scientist, Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Dr. Thomas D. Meyer, PhD, Associate Professor, Director of the Psychological Intervention and Research Laboratory for Mood Spectrum Disorders, Department of Psychiatry and Behavioral Sciences, McGovern School of Medicine, University of Texas HSC at Houston, Houston, TX, USA

Prof. Steven H. Jones, PhD, Co-Director Spectrum Centre for Mental Health Research and Professor of Clinical Psychology, Lancaster University, UK

Professor Mark R Baker MD, FRCP Director, Centre for Clinical Practice, the National Institute for Health and Care Excellence, 10 Spring Gardens, Trafalgar Square, London SW1A 2BU

We wish to respond to the points raised by Jauhar and colleagues in their Personal View published online on 4 February 2016.[1] We will outline how the NICE guideline on bipolar disorder[2] was developed, following the process established by the National Institute for Health and Care Excellence (NICE). Notably, this process differs from the development of a Cochrane meta-analysis and, indeed, many other guidelines. We then address six specific points raised by Jauhar and colleagues.[1]

The scope for the NICE guideline on bipolar disorder was developed by the National Collaborating Centre for Mental Health (NCCMH) and NICE with stakeholders drawn from a multidisciplinary group of clinicians from mental health, primary and social care, service users and carers, and members of professional and voluntary sector organisations. In this and almost all NICE guidelines, the scope was not confined to a single outcome; instead, stakeholders identified a range of outcomes in relation to symptoms, relapses, function, quality of life, and cost effectiveness. The NCCMH then worked with a Guideline Development Group (GDG) to define the review questions covering all areas specified in the scope, which included questions about treatment effects as well as questions that typically cannot be answered by synthesising randomised controlled trials (RCTs), for example about diagnosis and side effects. The GDG comprised practitioners and researchers from varied backgrounds, including secondary mental health care, primary care and social care, as well as service users and carers.

In line with the NICE guidelines manual,[3] it is the responsibility of the GDG chair, the guideline facilitator, the NCCMH technical team, the NICE technical support unit, the stakeholders (both during scope and guideline consultation), the NICE Commissioning Manager and the NICE Guidance Executive to monitor and eliminate allegiance (and any other) bias from any interested parties. All members declared relevant conflicts of interest or stated that they had none; these declarations were updated at every meeting and they are included in the published guideline. Each member of the GDG agreed to comment on evidence using their own expertise, and they agreed not to represent any outside organisation.

The GDG met regularly over an 18-month period. They developed recommendations that were informed by systematic reviews of the evidence, including meta-analyses of RCTs and syntheses of other studies where appropriate (documented in the full guideline[2]), as well as their own personal and professional expertise, and their values and preferences. Initial meetings of the GDG considered issues such as inclusion and exclusion criteria for studies. In later meetings, the GDG interpreted evidence presented by the review team. Further checks on the process included (i) observation of every meeting by NICE to ensure consistency across all NICE guidelines, (ii) peer review and challenge by pre-registered stakeholders, (iii) national and international peer review, and (iv) a quality assurance review conducted by methodology and subject experts convened by NICE. Minutes of every GDG meeting were taken, and reasons for why certain decisions were made were recorded in the full guideline (in the 'From evidence to recommendations' sections[2]). Evidence consulted by the GDG is fully documented in the guideline, and readers who want to see the review protocols, statistical code, meta-analyses (including the data as we entered them), study characteristics,

risk of bias assessments, GRADE profiles, etc., can find the full guideline, including 36 appendices, on the NCCMH website (http://www.nccmh.org.uk/ab_CG_BD_Up.html).

The NICE guideline on bipolar disorder was written to reflect a recovery-orientated approach as was indicated by the NICE guideline on service user experience.[4] The recommendations provide a starting point to guide clinicians in making decisions collaboratively with service users and carers. The GDG was aware that NICE guidelines have an important influence on the availability of resources and future research. Consequently, it aims to inform decisions about current services, and to identify pressing questions for improving the treatment of bipolar disorder. It acknowledges uncertainty and heterogeneity in treatment effects, and it suggests that choices should be made based on the best available evidence regarding safety, effectiveness, and cost, as well as service user, carer, and stakeholder preferences.

After reviewing the evidence, the GDG's expert assessment was that there is some evidence of benefit for both psychological and pharmacological interventions, and although there are important limitations in the evidence for both types of treatment, service users (and their families and carers) who want access to these services should be able to access them. Recommending psychological interventions does not favour one modality, and it does not imply that psychological should replace pharmacological interventions; they are not mutually exclusive. The guideline recommends that all people with suspected bipolar disorder should be assessed in secondary mental health care and that pharmacological treatment should be initiated there. In England, psychological interventions for bipolar disorder are available in primary or secondary care depending on locality. Therefore, the NICE guideline on bipolar disorder reflects the organisation of National Health Service (NHS) care in England, and the NICE quality standard for bipolar disorder[5] recognises that psychological interventions are not currently universally available.

Jauhar and colleagues state that they contacted NCCMH and received no response. None of the Guideline Development Group was contacted directly and we can only assume that Jauhar and colleagues attempted to make contact via the NCCMH website. The authors of the guideline would have been happy to explain the guideline development process, and to correct several misunderstandings, if Jauhar and colleagues had contacted us directly. Instead, we take six specific points raised by Jauhar and colleagues[1] and address them in turn here:

1. We did not 'correct for multiple comparisons'

The NICE guideline on bipolar disorder includes many meta-analyses because multiple interventions have been evaluated for treating acute episodes (mania and depression) and for preventing future episodes; these interventions have been compared with multiple other interventions for multiple outcomes at multiple time points. Jauhar and colleagues point to these difficulties in evaluating psychological interventions, but evaluations of pharmacological interventions are similarly complicated. They do not suggest a way to reduce the number of comparisons, and their proposal to correct for multiple comparisons would, as Schultz and Grimes state in their 2005 Review on multiplicity in randomized trials,

"sabotage interpretation"; the proposed Bonferroni correction would have been inappropriate because endpoints were related and not independent in the reviews of both psychological and pharmacological interventions.[6]

In the context of guideline development, reducing the number of outcomes would not have addressed the concerns raised during the scoping phase of the development of the guideline by stakeholders, who favoured a recovery-based approach to care that considered all aspects of care including symptoms, function, acceptability, adverse effects, and quality of life. Including these outcomes (and related meta-analyses) was necessary to respond to the scope.

2. We pooled data on different types of psychological interventions

Where there are many available interventions and comparators, pooling them is one way to reduce the number of comparisons in a systematic review. Jauhar and colleagues[1] appear to be undecided about the best way to conduct a review in this complex area (that is, by pooling interventions or reporting all comparisons as they were originally described). Like others,[7] the GDG concluded that empirically evaluated psychological treatments were broadly similar in content, and therefore made recommendations according to the form of delivery (individual, family and group) and indication (acute and long-term treatment).

3. We recommended CBT and psychoeducation for bipolar depression, but the evidence does not support this

Overall, the meta-analyses undertaken for the NICE guideline on bipolar disorder found evidence that individual acute treatment improved acute depression symptoms, and the guideline describes limitations in the quality of the evidence.[2] What's more, a purpose of psychological therapies and psychoeducation is to help service users (and their families and carers) understand what to expect with bipolar disorder and how they can cope with it. The GDG also noted that bipolar depression is so similar to unipolar depression that the disorder is often misdiagnosed for many years. Given the purpose of psychological therapies, and given robust evidence of the effectiveness of CBT and other psychological treatment approaches for unipolar depression, the GDG decided to recommend a choice of individual high-intensity or bipolar-specific psychological treatment for the acute management of depression symptoms.

4. We excluded a large trial from one analysis

It was decided at an early GDG meeting to consider RCTs for long-term pharmacological or psychological treatment. For long-term management, the GDG decided to consider trials with a duration of at least 12 months in which participants were euthymic at baseline (see the protocol for psychological interventions in the full guideline, p. 251[2]), and the GDG separately considered outcome in trials including people who were acutely depressed or acutely manic. That is, the GDG distinguished between pharmacological and psychological interventions for (i) the treatment of acute episodes, and (ii) long-term management.

Scott and colleagues[8] included a mix of participants who were euthymic and participants who were depressed. The published report did not distinguish (i) relapse for participants who were euthymic from (ii) effects for participants who were depressed. The GDG wrote to Professor Scott who was the chief investigator of this publicly funded RCT asking for more detail. Professor Scott declined to provide any more data at that time as she felt this "may jeopardise future publications". The meta-analysis shown by Jauhar and colleagues[1] should be interpreted with caution because only 171 participants were in remission at the time of randomisation;[8] the real treatment effect may differ depending on what phase participants were in when they began the study, and it is unclear how many people who were really "at risk" of this outcome experienced it. Including the study, Jauhar and colleagues[1] find a non-significant result, which is not evidence of "no effect" or a "negative result" as they incorrectly claim. The published guideline also included results for different types of relapse (manic and depressive); additional analyses are included in Appendix 25,[2] which reports the published data about specific types of relapse at different times.

Although not included in the particular meta-analysis cited by Jauhar and colleagues,[1] the GDG was aware of this study, discussed its implications, and considered the overall quality of the evidence in making their recommendations.

5. We recommended psychoeducation for relapse prevention, but the evidence does not support this

Meta-analyses of RCTs are a component of evidence-based practice, and meta-analyses were one source of information used by the GDG. Members of the GDG also concluded, based on other evidence and based on their own experience and expertise, that psychological interventions serve purposes not captured in meta-analyses of RCTs, including providing information and support to people in need. The GDG was aware of methodological limitations in the available meta-analyses, and they were aware that the evidence was not all positive. They considered those limitations and inconsistencies, and they drew appropriately circumscribed conclusions. For example, no specific form of therapy emerged as a "gold standard", so the GDG decided to make general rather than specific recommendations about treatment strategies. Just as recommendations for pharmacological interventions may change if new interventions are developed or new evidence emerges about existing interventions, more specific recommendations about psychological interventions may be possible in future guidelines if there is more empirical evidence available for psychological interventions.

6. The guideline ignored limitations in the quality of the evidence for psychological interventions.

Like the evidence for pharmacological interventions for bipolar depression and long-term management, studies of psychological interventions made different comparisons and, in many cases, could not be combined for analysis. Most of the evidence for psychological interventions came from small studies, and the resulting analyses were limited in quality, so

the guideline states that most evidence was low or very low quality.[2] The GDG acknowledged uncertainty throughout the guideline and concluded that "[psychological interventions] might improve symptoms and reduce the risk of relapse and hospital admissions", noting that the "evidence varies in quality".[2] The GDG also made recommendations to improve the overall quality of research in this area, and they recommended research that could substantially inform, and possibly change, recommendations in future versions of guideline.

The guidelines applied the same criteria for pharmacological and psychological interventions for bipolar disorder, and the GDG evaluated the strengths and limitations of evidence for both approaches. The GDG made recommendations to improve clinical practice on the basis of the best evidence that we could obtain at the time. Critics might argue that GDGs should make recommendations based only on high-quality evidence, in which case there would be few recommendations for either the pharmacological or psychological treatment of severe mental illness. It is the opinion of the GDG, stakeholders, peer reviewers and NICE that this would have been an unreasonable approach. We certainly hope that subsequent versions of this guideline will be served by a more substantial and higher quality evidence base for all interventions.

Acknowledgments

Thanks to Dr Clare Taylor, Associate Director for Quality and Research Development, NCCMH, and Nuala Ernest, Associate Editor, NCCMH, London, UK.

References

1 Jauhar S, McKenna PJ, Laws KR. NICE guidance on psychological treatments for bipolar disorder: searching for the evidence. *Lancet Psychiatry*. Published online 4 February 2016. DOI: http://dx.doi.org/10.1016/S2215-0366(15)00545-3.

2 National Collaborating Centre for Mental Health. Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care, updated edition. Clinical guideline 185. [Full guideline]. London: The British Psychological Society and The Royal College of Psychiatrists, 2014.

3 NICE. The Guidelines Manual. Process and Methods Guide 6. London: NICE.

4 National Collaborating Centre for Mental Health. Service user experience in adult mental health: improving the experience of care for people using adult NHS mental health services. Clinical guideline 136. [Full guideline]. London: The British Psychological Society and The Royal College of Psychiatrists, 2012.

5 National Institute for Health and Clinical Excellence. Bipolar disorder in adults. Quality standard 95. London: NICE, 2015. Available from: https://www.nice.org.uk/guidance/qs95. Accessed 9 February 2016.

6 Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005; **365:** 1591–95.

7 Miklowitz DJ, Goodwin GM, Bauer MS, Geddes JR. Common and specific elements of psychosocial treatments for bipolar disorder: a survey of clinicians participating in randomized trials. *J Psychiatr Pract.* 2008; **14:** 77–85.

8 Scott J, Paykel E, Morriss R, et al. Cognitive–behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry* 2006; **188:** 313–20.