Modelling suicide in bipolar disorders: limitations and opportunities

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In their paper in this issue,[1] Malhi et al highlight a key clinical area; whilst suicide rates are increased in general in those with mental health problems, they are particularly high in bipolar disorder, with a prevalence up to 30 times greater than in the general population. This is a topical issue, recently discussed in a viewpoint article in JAMA,[2] where the course of bipolar disorder was compared with the development and spread of a malignancy. Although this analogy might at first sight seem extreme, both conditions are life-threatening, with significantly increased mortality rates. Despite this knowledge, and the data supporting the benefit of intensive treatment early in the course of bipolar disorder, a first episode of mania is often treated less intensively than evidence-based guidelines would recommend. This, combined with rates of 50% non-adherence to medications after first manic episode, contributes to poorer course of illness and long-term outcome. Unlike in cancer care, there is a relative paucity of treatment RCTs in bipolar disorder, complex combinations of treatment in resistant patients are not well studied and the causes and prevention of suicide and increased mortality rates in general are not well characterised.

In their paper, Malhi et al carried out a narrative review of the literature of published models of the processes contributing to the increased rate of suicide in bipolar disorder. Whilst their search is wide and inclusive in scope, the lack of a systematic approach limits its replicability and the conclusions that can be drawn from it. For example, there are no details of the methods used in the search, the numbers of papers retrieved and the reasons for and against inclusion. On the basis of their results, the authors have used the different models of suicidal behaviour in bipolar disorder to form a new integrated model incorporating recent research. The model is hypothetical and limited by its lack of evidence base and systematised searching, but it is helpful in suggesting components of the suicide process that are potentially measurable in future research. It also suggests areas where research might focus specifically on strategies to reduce suicidal behaviour in this high risk population.

Previous research on suicidal behaviour in bipolar disorder has been limited by methodological difficulties. So, for example, the combined evidence for the anti-suicidal effects of lithium when taken

together is convincing[3]. However, this evidence comes from combining different studies, none of which individually are ideally designed to answer the questions of whether lithium reduces suicidal behaviour and if so how it produces this effect. RCTs are methodologically the gold standard, but the individual RCTs of treatments in bipolar disorder have been relatively small, have focussed primarily on efficacy and have reported suicidal behaviour as a rare incidental finding rather than a primary outcome. These individual RCTs are unlikely to have sufficient power to assess any association of suicidal behaviour with treatment. Pooling data through the use of meta-analysis allows for issues such as low event rates to be addressed, but even so, the numbers are small [4]. In general, the low baseline rate of suicide (a relatively rare event) makes it difficult to show a difference between treatment arms in RCTs [5]. The low baseline rate of suicidal behaviour in general may be even lower in trials as suicidal patients are often excluded [3], as are those with co-morbidities which can increase risk of suicidal behaviour [6]. Observational studies have the advantage of including much larger numbers and are helpful in supporting or refuting the combined data from RCTs, but are methodologically less robust and may be more prone to bias.

New research needs to focus on RCTs, which specifically investigate suicide in high risk populations such as those with bipolar disorder. Ethical issues of placebo allocation can be overcome by additive designs, such as comparing antidepressant alone versus antidepressant plus lithium, so that all treatment arms have active treatment. The revised model proposed by Malhi et al suggests new areas for research to elucidate further the mechanisms by which this behaviour evolves. Studies which focus specifically on populations at high risk of suicide with targeted interventions will show us further what preventative strategies might be effective (even though studies in this area are very difficult to carry out, especially in young people[7]). Because of the power issue non-fatal suicidal behaviour will probably have to be the primary outcome.

Malhi et al also highlight a key issue in studying suicidal behaviour in general, which is relevant also to bipolar disorder. Although risk factors can be highlighted, it is difficult to predict times of specific

increased risk. Suicide is an event that is a culmination of many contributing factors. How and when these factors will interact is difficult to anticipate. Whilst the use of screening tools used to assess the risk of self harm might seem appealing, these perform no better than clinician or patient ratings of risk [8]. Indeed, as Malhi et al point out, not all patients with bipolar disorder and identifiable risk factors have engaged in suicidal behaviours, and many patients express suicidal ideation but do not make suicide attempts. On the other hand, many patients who eventually die by suicide have done so without communicating any suicidal ideation to their clinical team [9]. In a meta-analysis of suicide risk, it was predicted that 95% of high risk patients will not die by suicide and that approximately 50% of suicides will occur in low-risk patients [10]. This reality is becoming apparent more generally in suicide risk factor studies in psychiatric patients. Given the considerable difficulty of identifying patients who are most likely to engage in a suicidal act, a more pragmatic approach is to treat *all* patients with bipolar disorder (and indeed with any psychiatric disorder) as at risk and to employ risk reduction strategies as part of routine clinical practice in all cases. This might include developing a dynamic risk formulation, including, for example, key factors which might alter risk in a patient (e.g. end of an unstable relationship), together with safety planning, such as what the patient can do in the event of a crisis (e.g. who can be contacted in the patient's social circle as well as clinically), restriction of access to means for suicide, communication with family and other key individuals, maximising the therapeutic aspects of the clinician-patient relationship, using evidence-based treatments wherever possible, and having clear therapeutic plans which are communicated to all key personnel involved in care (including of course the patient him- or herself).

In conclusion, the paper by Malhi et al is an interesting contribution to the growing debate of how to reduce risk of suicidal behaviour and suicide in the high risk group of people with bipolar disorder, but, understandably, it clearly raises more questions than it answers. By highlighting the malignant course of bipolar disorder and its increased mortality rate, this review poses important research questions, which will have direct clinical significance.

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