

NHMRC Australia Fellowship 569738 award to Professor Wayne Hall 2009-2013 postprint

Carter, A., & Hall, W. (2013). Managing suicide risk in experimental treatments of treatment-resistant depression. *AJOB Neuroscience*, 4(1), 38-39. doi: 10.1080/21507740.2012.748706

Gilbert (2013) asks whether patients with treatment-resistant depression (TRD) who have a history of suicide attempts or thoughts (suicide-related behavior, SRB) should be excluded from trials of deep brain stimulation (DBS) because of suggestive evidence that DBS may increase the risks of suicide in these patients. Gilbert's suggestion raises two questions, one scientific and one ethical: Is there sufficient evidence to conclude that DBS in fact increases the risk of SRB in TRD patients? If there were such evidence, would it warrant the exclusion of TRD patients reporting past SRB from trials of DBS?

There is a major scientific challenge in assessing whether DBS increases the risk of SRB in patients with treatment resistant depression, namely, that much larger patient samples are required than are currently available if we are to distinguish between the rates of SRB in TRD patients treated with DBS and those not so treated. The studies that Gilbert cites are insufficiently powered to show whether DBS can increase the risk of suicidal behavior. These studies of between 11 and 20 individuals report SRB prevalence rates of 9–12%. These rates are not remarkably different from those in individuals with TRD who have not undergone DBS (approximately 15%) (Isometsa et al. 1994; Wulsin, Vaillant, and Wells 1999).. The impact of DBS on SRB warrants careful scrutiny in future trials, but the available evidence does not establish that DBS has increased the rate of these events over and above the baseline rate in TRD. Given that DBS will probably remain an experimental technology for TRD that is employed in small patient samples for some time, it is unlikely that we will soon have data from large enough samples to decide whether DBS increases suicide or not.

The relevance of studies of the rates of SRB in patients who have undergone DBS for indications other than TRB is unclear. SRB has been reported in Parkinson's disease (PD) patients who have undergone DBS, but in the largest study to date ( $n = 5,311$ ), the rate of suicide was only 0.45% (Voon et al. 2008). This is significantly less than the higher rates reported in the small studies of DBS in TRD patients, but it is difficult to interpret such comparisons because of the very different patient population and different sites of stimulation in the brain.

Even if research shows that DBS elevates suicide risk in some TRD patients, this may not necessarily justify exclusion of patients with a history of SRB from trials of DBS. DBS of TRD already carries significant risks that are seen, by some at least, as justified by the benefits that the treatment may bring. While the risk of DBS-induced suicide should not be ignored, it needs to be considered against the other serious risk of harm associated with the procedure. A recent meta-analysis found that around 11% of patients who undergo DBS will suffer serious or irreversible harms, including a life-threatening intracerebral hemorrhage, permanent cognitive or motor impairment, and brain infection (Kleiner-Fisman et al. 2006).

The potential harms of not treating an individual with TRD must also be considered. These risks include suicide because patients with TRD have by definition exhausted all available treatment options, apart from DBS. Indeed, it is their suicide risk that is often used to justify trialing DBS in this condition. Excluding patients with a history of suicidal thoughts or behavior would therefore arguably reduce the strength of the ethical

warrant for trialing DBS in TRD patients. Retrospective self-reported suicidal behavior is also not a reliable predictor of future suicidal behavior, with one study showing that of a sample of patients that committed suicide, the majority (78%) of those admitted for suicidal ideation denied any previous suicidal ideation when asked (Busch, Fawcett, and Jacobs 2003).

We agree with Gilbert that more analysis is needed of ethical issues in deciding who to include in and exclude from trials of DBS in TRD, as well as other psychiatric disorders. Excluding persons who are acutely suicidal or severely cognitively impaired seems a defensible first step, but excluding all TRD patients who have reported suicidal thoughts or behavior in the past could deny many of these patients access to a clinical trial that may potentially benefit them.

Additional challenges need to be addressed in the ethical recruitment of subjects into trials of DBS for TRD and other psychiatric disorders. These include managing unrealistic patient expectations about the likely effectiveness of the treatment; ensuring that they appreciate the risks of the intervention; and ensuring that patients have the cognitive and motivational capacities to provide free and informed consent to study participation (Carter et al. 2011)

Patients who do not improve after DBS will probably be at greatest risk of suicide because they have failed to benefit from the treatment of last resort. This view is supported by studies showing that those who are unresponsive to DBS for TRD are more likely to develop postoperative SRB (Bewernick et al. 2012; Kennedy et al. 2011). This issue will need to be addressed in the study design and recruitment of participants into trials of experimental treatments for a life-threatening condition (Carter, Bartlett, and Hall 2009).

We agree with Gilbert that there is a possibility of increased SRB in patients treated with DBS for TRD, but much larger studies and meta-analyses will be required to assess whether DBS increases the risk of suicide. While such information will be critical for patients and physicians making a balanced assessment of the risks and benefits of DBS, we do not think that a history of SRB should necessarily be an exclusion criterion. We nonetheless strongly agree with Gilbert that DBS remains an experimental treatment in TRD, regardless of its evident success in treating neurodegenerative movement disorders. We therefore endorse his call for greater attention to adverse effects of this treatment and better studies of rates of longer term adverse effects, including suicide, in trials of DBS (Hall and Carter 2011).

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