Misrepresenting harms in antidepressant trials- more evidence from Clinical Study Reports.

Joanna Moncrieff,

Senior Lecturer,

Division of psychiatry,

University College London,

Maple House,

149 Tottenham Court Road,

London,

W1T 7NF.

E mail address: j.moncrieff@ucl.ac.uk

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People in the United Kingdom are consuming more than four times as many antidepressants as they were two decades ago (1). Despite this, we still do not fully understand the effects of these drugs, nor can we be confident about their risk-benefit ratio.

Unresolved issues include the nature and frequency of potential serious adverse effects such as self-harming or suicidal actions, suicidal ideation and aggression. In the linked paper, Sharma et al use Clinical Study Reports (CSRs) to explore these adverse effects. CSRs are prepared by pharmaceutical companies for the purpose of obtaining marketing authorisation. There are guidelines about contents and presentation of CSR's (2) but no mandatory requirements. Consequently, although CSRs usually contain more data than published articles (3), the level of detail varies. Moreover, there may be differences between what is reported in the body of the CSR and data contained in appendices, such as individual patient listings of adverse events or narratives of serious adverse events.

Sharma et al's analysis of CSRs reveals misrepresentation of adverse events. Comparing the 'results' reported in CSRs with data from individual patient listings or patient narratives revealed misclassification of deaths on antidepressants, and misrepresentation of suicidal events. More than half of the suicide attempts and instances of suicidal ideation were coded as 'emotional lability' or 'worsening of depression,' for example. Summary reports published on Eli Lilly's website were found to be even more incomplete, listing only 10% of the suicide attempts revealed in the corresponding CSRs, and no instances of suicidal ideation.

Over half of the CSRs selected by Sharma et al had no individual patient listings, this data having been withheld. This begs the question of how many more adverse events would have been revealed if individual patient listings were available for all trials, and raises concerns about why this information is allowed to be withheld.

The current review is consistent with other evidence pointing to an increase in suicidal behaviour and ideation among children and adolescents taking selective serotonin reuptake inhibitors (SSRIs) (4). The paper by Sharma et al is the first large-scale, quantitative analysis to demonstrate an increase in aggressive behaviour in this age group. The analysis did not detect an increase in suicide, suicide attempts, suicidal ideation or aggression in adults and meta-analyses of data on adults remains conflicting (5; 6). Early case reports, published

before the issue became controversial, document occurrence of these effects in adults, however, and also provide evidence as to the mechanism of these effects. These reports describe a state of agitation, somewhat similar to the akathisia produced by antipsychotics, associated with intense and violent suicidal preoccupation (7). However, as Sharma et al demonstrate, recording of 'akathisia' in antidepressant trials remains inconsistent and unreliable, hence we have little idea of the frequency of this effect.

Although 'activation' effects (or akathisia) are recognized, there is little acknowledgement that antidepressants have mind-altering properties that are independent of their supposed effects on underlying mental disorders. One study revealed various changes to emotions and behaviour in patients taking antidepressants, which were associated with suicidal ideation (8). Evidence suggests there can be severe and sometimes prolonged withdrawal syndromes (9). With some exceptions (10), however, we lack the detailed exploration through animal behaviour and healthy volunteer studies that might clarify the range, nature and duration of the alterations that antidepressants induce.

Despite their widespread use, antidepressants are only modestly more effective than placebo in trials of depression. Measures of global clinical improvement suggest the difference is not clinically relevant or even detectable (11). Moreover, placebo-controlled studies do not distinguish whether the effects of a drug are attributable to the targeting of putative underlying mechanisms, or a consequence of the drug's mind-altering effects. The blunting of emotions produced by SSRIs may directly affect depression rating scale scores, for example, and their psychoactive and physical effects may influence patient expectations, promoting an amplified placebo effect (12).

With doubts about the efficacy and effectiveness of antidepressants, and evidence that they can produce such serious adverse reactions as suicidal and aggressive tendencies, regulators and the public need access to more comprehensive and reliable data. The results reported in CSRs, on which decisions about market authorization are based, are likely to underestimate the extent of drug-related harms. We need access to original data from trials, but we also need more research that addresses the whole range of antidepressant-induced behavioural, emotional and physical alterations with acute treatment, long-term use and following withdrawal.

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Competing interest statement:
I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: I have no competing financial interests. I am co-chair person of the Critical Psychiatry Network.

Reference List

(1) Sweet D. Health. A report of the Office for National Statistics. Social Trends 2011;41:1-36.

(2) International Conference on Harmonisation. Structure and Content of Clinical Study Reports, E3. Geneva: International Conference on Harmonisation; 1996. Report No.: E3.

(3) Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervolgyi V, Kohlepp P, et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. PLoS Med 2013 Oct;10(10):e1001526.

(4) Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004 Apr 24;363(9418):1341-5.

(5) Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880.

(6) Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005 Feb 19;330(7488):396.

(7) Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. J Clin Psychiatry 1991 Dec;52(12):491-3.

(8) Goldsmith L, Moncrieff J. The psychoactive effects of antidepressants and their association with suicidality. Curr Drug Saf 2011 Apr;6(2):115-21.

(9) Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. Psychother Psychosom 2015 Feb 21;84(2):72-81.

(10) Tranter R, Healy H, Cattell D, Healy D. Functional effects of agents differentially selective to noradrenergic or serotonergic systems. Psychol Med 2002 Apr;32(3):517-24.

(11) Moncrieff J, Kirsch I. Empirically derived criteria cast doubt on the clinical significance of antidepressant-placebo differences. Contemp Clin Trials 2015 Jul;43:60-2.

(12) Moncrieff J, Cohen D. Do antidepressants cure or create abnormal brain states? PLoS Med 2006 Jul;3(7):e240.