Risk of suicidal behaviour in adults taking antidepressants

Increased risk is probably restricted to younger people and varies greatly between individual medicines

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Antidepressant drugs currently carry warnings of the possibility of increased suicidal ideation and behaviour during treatment, especially in younger patients. In the linked meta-analysis, Stone and colleagues report on the possible link between the risk of suicide and antidepressants using data on individual patients from placebo controlled trials.[1] This analysis of 372 placebo controlled antidepressant trials and nearly 100 000 patients found that the association between antidepressant drugs and the incidence of reported suicidal behaviour is strongly related to age. The risk was raised in people under 25, not affected in those aged 25-64, and reduced in those aged 65 and older. The analysis also found differences in risk between drugs.

This analysis is not new—it was published fully on the Food and Drug Administration (FDA) website more than two years ago.[2] It was widely covered at the time in the international medical press and led to warnings being included on datasheets.[3-6] Because the analysis has not been updated since the initial publication and the present report selectively reports the full analysis, it raises the question of why it is being published in the *BMJ* now, more than two years later. Its objective is to make a summary of these important results more widely available in a way similar to the publication in the *BMJ* of summaries of Cochrane reviews.

Other meta-analyses had already been performed, but this analysis was a methodological advance because it used individual patient data from the trials, and suicidal events were reclassified according to a common system to increase the reliability of the results.[7 8]

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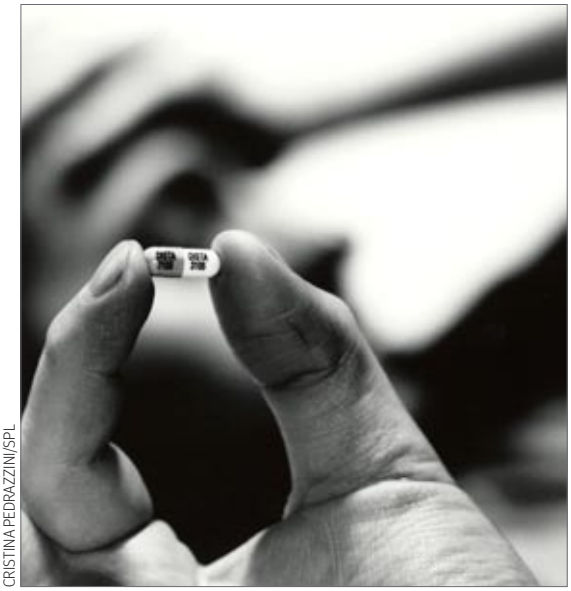
None the less, important limitations remain because of the characteristics of the primary trials. A standard exclusion in placebo controlled trials of antidepressant drugs is that severely ill patients, especially those who are actively suicidal, are not enrolled. This probably leads to very low numbers of completed suicides in these trials. If such trials aim to provide evidence of the clinical effects of the investigational drug, then this exclusion is as clinically illogical as excluding patients with a high risk of mortality in trials in oncology or cardiology. It makes it impossible to estimate the potential benefits of a reduction in baseline suicidality.[9]

Furthermore, the low event rate of completed suicide means that retrospective analyses have to broaden the definition of suicide beyond completed suicides to gain sufficient statistical power. Regardless of how much effort is put into developing standardised reclassifications, the fundamental uncertainty about the validity and meaning of a composite outcome that was not prespecified in the primary trials remains.

The review procedures showed some lack of transparency, as sometimes happens in analyses conducted by regulatory authorities.[10] It is unclear why optimal methods of meta-analysis of systematic review—for example, prior pre-review and publication of the protocol, unselective reporting of the outcomes—were not used. One way of ensuring adherence to currently optimal guidelines for systematic reviews would have been to conduct the analysis under the auspices of the Cochrane Collaboration. Although meta-analyses of individual patient data could usefully look at important clinical outcomes other than suicidality, the Cochrane database still contains few meta-analyses of individual patient data.

Could it be that companies are willing to release individual patient data only when required to by regulatory agencies who grant the marketing authorisations of drugs? If that is the reality, then the true collaboration between regulators and other agencies, which seems to be the FDA's new aim, could be a powerful approach to synthesising clinical knowledge.[11] In particular, the age related decrease in risk for suicide, which seems to be inversely paralleled by increasing efficacy with age, could be investigated further with individual patient data from these trials.[5]



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Finally, we should consider these results alongside other recent evidence on antidepressants in major depression. Although this report focuses on age related differences in the risk of suicidal behaviour, individual drugs seem to show some important differences. The odds of suicidal behaviour on sertraline, for example, is around half that on placebo. In comparison, citalopram and escitalopram seem to increase the risk of suicidal events.

Unfortunately, the analysis did not include indirect comparisons (which would have been possible by virtue of the common placebo comparator) when comparing drugs, so that any conclusions about the differential effects of treatments must be made with caution. None the less, it is becoming apparent that antidepressants vary in both their efficacy and adverse effects. A recent multiple treatments meta-analysis that compared the efficacy and acceptability of antidepressants showed meaningful differences between drugs.[12] That analysis found sertraline and escitalopram to have the best balance of short term efficacy and tolerability. Taking the results of the analyses together reinforces the view that sertraline has a highly favourable profile in terms of efficacy, acceptability, and safety. Although different mechanisms might lead to clinical relief of symptoms and increased suicidality (perhaps via increased agitation), a more likely mechanism for the effects of sertraline is that it is simply better tolerated and more likely to be effective, hence reducing both depressive symptoms and suicidality.

1 Stone MB, 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.
2 Laughren TP. *Briefing document for December 13 meeting of Psychopharmacologic Drugs Advisory Committee*. 2006. www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf.
3 Friedman RA, Leon AC. Expanding the black box—depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007;356:2343-6.
4 Kuehn BM. FDA panel seeks to balance risks in warnings for antidepressants. *JAMA* 2007;297:573-4.
5 Barbui C, Cipriani A, Geddes JR. Antidepressants and suicide symptoms: compelling new insights from the FDA's analysis of individual patient level data. *Evid Based Ment Health* 2008;11:34-5.
6 Leon AC. The revised warning for antidepressants and suicidality: unveiling the black box of statistical analyses. *Am J Psychiatry* 2007;164:1786-9.
7 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385.
8 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;330:396.
9 Cipriani A, Barbui C, Geddes JR. Suicide, depression, and antidepressants. *BMJ* 2005;330:373-4.
10 Vitry A, Lexchin J, Sasich L, Dupin-Spriet T, Reed T, Bertele V, et al. Provision of information on regulatory authorities' websites. *Intern Med J* 2008;38:559-67.
11 Hamburg MA, Sharfstein JM. The FDA as a public health agency. *N Engl J Med* 2009;360:2493-5.
12 Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746-58.

Diagnosis of venous thromboembolism

D-dimer tests can help management but cannot replace clinical judgment

RESEARCH, p 450

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Because the signs and symptoms of deep venous thrombosis and pulmonary embolism are common but non-specific, they often present a diagnostic challenge. Both underdiagnosis and overdiagnosis are associated with substantial morbidity and mortality.

D-dimers are fibrin degradation products resulting from endogenous fibrinolysis associated with intravascular thrombosis. A non-specific increase in D-dimer concentration is seen in many situations, precluding its use for diagnosing venous thromboembolism (VTE). However, a low D-dimer concentration is thought to rule out the presence of circulating fibrin and therefore VTE. Early enzyme linked immunosorbent assay D-dimer tests took a long time to do, limiting their usefulness in acute care. Second generation assays provide results within an hour, and point of care tests produce results within 10-15 minutes.

In the linked systematic review and meta-analysis, Geersing and colleagues analysed the diagnostic performances of several qualitative and quantitative D-dimer tests used at the point of care.[1] They found that quantitative tests perform better than qualitative ones, but that the number of studies was limited. Their results also confirmed the value of a negative D-dimer result in excluding a diagnosis of VTE and pulmonary embolism, but they make several interesting points.

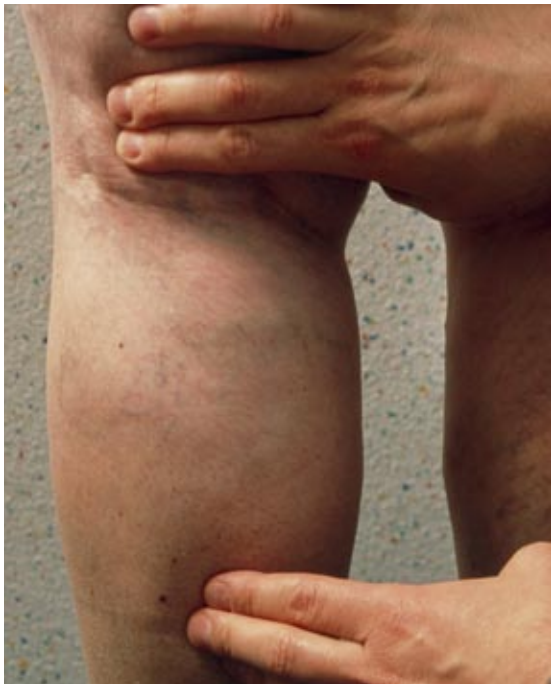
Firstly, in point of care testing, as in the laboratory, diagnostic performance depends on the assay technology.[2-4] Secondly, some tests are still imprecise. In particular, quantitative tests used at the point of

care have been poorly evaluated in patients with suspected pulmonary embolism. More importantly, none of these tests reliably ruled out VTE without taking into account the clinical probability of the disease. The clinician's estimate of the pretest probability of a target disorder is a crucial determinant of the direction and extent of the diagnostic work-up.

The authors used Bayes's theorem to calculate the probability of VTE, conditioned by the likelihood ratio as a function of the pretest probability. For this purpose, they assumed a test threshold probability of 2%, below which further testing was not warranted. They found that for all tests apart from the Cardiac D-dimer test, pretest probability had to be below 8-10% to rule out VTE with confidence when point of care D-dimer testing was negative.

Point of care D-dimer tests are particularly useful for doctors who need rapid information while on the move. Negative results may eliminate the need for further diagnostic testing in almost 30% of patients with suspected VTE. However, in day to day practice, such easy tests carry some risks too; for example, D-dimer tests are sometimes ordered in patients with an obvious explanation for their signs and symptoms.

In the best case scenario the D-dimer test will be negative with just the loss of a little time and money, but in the worst case scenario, a positive D-dimer test will prompt the doctor to order further testing, such as leg vein ultrasonography or computed tomography (or both), which carry risks of iatrogenic events and false positive results. The decreasing prevalence of cases in the diagnostic studies published during the past decades illustrates the evolution of the implicit threshold used by doctors when ordering tests.[5] Of note, this prevalence was as low as 3-4% in the more recent studies included in Geersing and colleagues' meta-analysis.[1] Moreover, in a French national observational study, doctors ruled out pulmonary embolism in 57% of cases on the basis of inappropriate criteria, exposing patients to a high risk of recurrent VTE. One of the most common reasons for inappropriate testing was the lack of evaluation of clinical probability.[6]



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So how do Geersing and colleagues' results translate into current practice? We have to follow some evidence based rules: to use tests with confirmed diagnostic performance; to consider different diagnoses and their clinical probabilities before performing any test; and to perform tests that will lead to a post-test probability low enough to rule out VTE if the result is negative or high enough to diagnose VTE if the result is positive. Several tools can help to achieve these aims, such as the PERC (pulmonary embolism rule-out criteria) rule, which can help decide who to test[7]; a clinical probability score that defines pretest probability more accurately[8 9]; and the diagram of Fagan, which can use the likelihood ratios of the tests to calculate post-test probabilities.[10]

Finally, the effect and cost of point of care D-dimer tests need to be evaluated in a randomised controlled cluster trial in which primary care doctors or emergency departments are provided or not provided with point of care D-dimer test facilities. However, one of the key points will be how doctors will apply Bayesian reasoning in day to day clinical practice. Computer based clinical decision support systems are a promising tool in such complex medical situations, and they may become another useful device for the point of care diagnosis of VTE.[11]

1 Geersing GJ, Janssen KJM, Oudega R, Bax L, Hoes AW, Reitsma JB, et al. Excluding venous thrombo-embolism using point of care D-dimer tests in outpatients: diagnostic meta-analysis. *BMJ* 2009;339:b2990.
2 Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004;140:589-602.
3 Roy PM, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. *BMJ* 2005;331:259.
4 Di Nisio M, Squizzato A, Rutjes AW, Buller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J Thromb Haemost* 2007;5:296-304.
5 Le Gal G, Bounameaux H. Diagnosing pulmonary embolism: running after the decreasing prevalence of cases among suspected patients. *J Thromb Haemost* 2004;2:1244-6.
6 Roy PM, Meyer G, Vielle B, Le Gall C, Verschuren F, Carpentier F, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Ann Intern Med* 2006;144:157-64.
7 Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:772-80.
8 Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003;349:1227-35.
9 Righini M, Le Gal G, Aujesky D, Roy PM, Sanchez O, Verschuren F, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet* 2008;371:1343-52.
10 Richardson S, Wilson M, Guyatt G. The process of diagnosis. In: Guyatt G, Rennie D, eds. *Users' guides to the medical literature. A manual for evidence-based clinical practice.* Chicago: AMA Press; 2002.
11 Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005;293:1223-38.

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We are very grateful to everyone who has helped us test *BMJ* pico and those who have told us what they think of it. One "piconeer," Tom Jefferson, clearly enjoyed the experience, "I wrote the abstract using a mixture of cut and paste from the main text of the article, edits, and rewrites of sections. My personal bias is that I love the discipline of summarising and abstracting, as it teaches you to identify what is vital and what is not. The pico format seems OK. The table summarising the main results was a joy to construct as it gave me the chance to tell the story straight."[4] And a reader cheered us with this rapid response: "I was amused to see that the 'pico' version of this article in the print journal was accompanied by an editorial coauthored by Shorten and Shorten."[5]

1 Groves T, Godlee F. Innovations in publishing *BMJ* research. *BMJ* 2008;337:a3123.
2 Schwartz LM, Woloshin S, Dvorin EL, Welch HG. Ratio measures in leading medical journals: structured review of accessibility of underlying absolute risks. *BMJ* 2006;333:1248.
3 Godlee F, Delamothe T, Smith J. Continuous publication. *BMJ* 2008;336:1450.
4 Jefferson T. Reflections of a piconeer. 2009. http://bmj.com/cgi/eletters/338/feb02_1/b392#208917.
5 Brandon HA. Small things. 2009. http://bmj.com/cgi/eletters/338/jun11_2/b2060#215534.