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LETTERS

SUICIDALITY AND AGGRESSION DURING ANTIDEPRESSANT TREATMENT

Author's reply to Dubicka and colleagues and Stone

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Dubicka and colleagues say that we are likely to harm young people when we point out that antidepressants increase the risk of suicide.[1 2] They consider it harmful that some young people will not start taking antidepressants because they think that these drugs do more harm than good. What is harmful is when these authors and other psychiatrists claim that these drugs protect against suicide despite the solid evidence we have to the contrary and the clear warnings from drug agencies. Dubicka and colleagues say that "It is well established that the undertreatment of depression in children and young people is linked to suicide" and refer to an observational study. There are many such studies, but they are all flawed.[3]

These authors say that our statement that antidepressants doubled the risk of suicide in children and adolescents is incorrect, and they argue that there is a "hugely important difference" between suicides and suicidal behaviour. There isn't. A suicide starts with a thought about suicide, which leads to preparations for suicide, a suicide attempt, and suicide. It should surprise no one that the risk factors for serious suicide attempts are similar to those for suicide.[4 5]

Their other arguments are also invalid. There is no need for additional "contextual information" to interpret our results; it is not relevant whether the drugs we studied are recommended by the National Institute for Health and Care Excellence (NICE) because the increased risk of suicide is a class effect and *The BMJ* is read outside the UK where other drugs are used. The fact that the most severely depressed and suicidal young people were often excluded from the trials is also irrelevant because the suicidal effect of these drugs is also seen in healthy volunteers.[3-7] We found that the drug companies had excluded people at risk of committing suicide in at least 63% of the trials we analysed (which were performed in children and in adults). If the companies had truly believed that their drugs could reduce suicides, they would not have excluded people at risk of suicide. Companies that believe they have a drug that can reduce heart attacks would not study it in young people who are not at risk of having a heart attack.

Dubicka and colleagues recommend close monitoring when young people are treated with antidepressants. This is a fake fix. People cannot be monitored every minute and suicide can occur very suddenly, when no one expects it—for example, just after the patient seemed to be happy and well.[3]

Stone from the Federal Drug Agency seriously misrepresents not only his own work but also a paper by one of his FDA colleagues, Thomas Laughren.[8-10] We wrote that "The FDA did not consider the limitations of the trials that we identified and introduced some of their own—for example, by only counting events within 24 hours after the randomised phase was over." With a hair splitting argument, Stone asserts that if a person attempted suicide before the 24 hours were over, the FDA followed up on this to see whether the person died. He misses the point, which is that withdrawal symptoms after stopping the trial drug may come more than 24 hours later and may lead to suicide.[3]

Using FDA trial data, Laughren found 22 suicides in 22 062 patients randomised to antidepressants, or 10 per 10 000,[9] whereas in the large FDA meta-analysis he chaired five years later, there were only five suicides in 52 960 patients, or 1 per 10 000.[11] Stone asserts that the 22 suicides include those that occurred in "both placebo and treated groups and during open label extensions and studies." This assertion is misleading. Laughren wrote in his paper: "Suicide was defined as all deaths categorized by the investigator as suicide that occurred during the short-term phase of these trials or within 30 days of stopping assigned treatment." Because the follow-up was the same for the placebo group as for the drug group, it is perfectly legitimate to perform a simple test on the suicides. There were only two suicides in 8692 patients taking placebo, which Laughren interprets thus: "There is obviously no suggestion of an excess suicide risk in placebo-treated patients." No, there isn't, but we wonder why Laughren didn't comment on the fact that there were four times as many suicides in people taking antidepressants as in those taking placebo (all ages included), and the difference was significant (P=0.03; our calculation). Furthermore, some of the trials that were included in the 2006 FDA meta-analysis had reported far more suicides than the five that the FDA reported,[3] so it is not a question of open label follow-up as Stone claims.

It is absolutely essential to include events up to 30 days after the randomised phase of the trials is over. In clinical practice,

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doses are often missed, which means that the patients may increase their risk of suicide because of withdrawal symptoms. Pfizer's trials of sertraline given to adults illustrate this. The FDA's meta-analysis from 2006 didn't find an increase in suicide, suicide attempts, or self harm combined (relative risk 0.87, 95% CI 0.31 to 2.48; FDA's table 30),[11] whereas Pfizer's own meta-analysis suggested a halving of this risk (0.52, 0.17 to 1.59) when only events that occurred up to 24 hours were included.[12] When Pfizer included events occurring up to 30 days after the randomised phase was over, these suicidality events increased by about 50% (1.47, 0.77 to 2.83).[12] A 2005 meta-analysis conducted by independent researchers using UK drug regulator data found a doubling in suicide or self harm with sertraline used in adults when events after 24 hours were included (2.14, 0.96 to 4.75; our calculation).[13] Like us, these researchers noted that companies had under-reported the suicide risk in their trials, and they also found that non-fatal self harm and suicidality were seriously under-reported compared with the reported suicides. There are many other reasons why the FDA seriously under-reported suicides.[3]

In my view, the use of antidepressants should be forbidden in children and young people, because they say that these drugs don't help them in placebo controlled trials,[3] and these drugs can cause serious harm.

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