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3 August 2023

Open letter to:

Managing Editor Mary K. Billingsley, mbillingsley@jaacap.org
Journal of the American Academy of Child & Adolescent Psychiatry

Editor Dost Öngür, jamapsych@jamanetwork.org
JAMA Psychiatry (previously Archives of General Psychiatry)

Call for retraction of three fraudulent trial reports of antidepressants in children and adolescents

We, a Professor emeritus and specialist in internal medicine with expertise in clinical trials, and 10 people who each lost a child or spouse to suicide as a direct consequence of being prescribed an antidepressant drug for a non-psychiatric condition, call for retraction of three fraudulent trial reports of antidepressants in children and adolescents.[1-3]

The trial reports seriously underreported suicide attempts, other suicidal events, and precursors to suicide and violence on active drug, and exaggerated the benefits of the drugs substantially.

We know this because independent researchers have compared the published trial data with the data in the clinical study reports of the placebo-controlled trials the drug manufactures submitted to the drug agencies to get approval for their drugs for use in depression in children and adolescents.

By retracting the fraudulent trial reports and explaining why in accompanying editorials, you will provide a much needed service to the scientific community and the world's citizens, which will reduce the risk of additional meaningless suicides in children and young people.

If you don't act, you will not only sully the reputation of your journals. You will also be seen as being complicit in future suicides caused by antidepressants as a direct harm of these drugs.

We provide below the most important facts, which should make it easy for you to retract the articles and explain why.

The evidence that antidepressants increase the risk of suicide

In 2004, the FDA introduced a black box warning on the label of antidepressants because the placebo-controlled trials had shown that the drugs increase the risk of suicide in children, adolescents and young people up to age 24. In an internal report from 2006, the FDA noted on page 37 that suicidal behaviour, defined as *preparation for suicide or worse*, had an odds ratio of 2.35 (95% confidence interval 1.35 to 4.09, P = 0.002) for this age group.[4]

FDA's analyses were primarily based on the extensive clinical study reports of the placebo-controlled trials the drug manufactures had submitted to the agency.

Despite the fact that many suicide events were missing in the trials,[5 (page 73 onwards)] the FDA's meta-analysis showed an increase in suicidal behaviour up to age 40 (pages 31 and 34 in its internal report):[4]

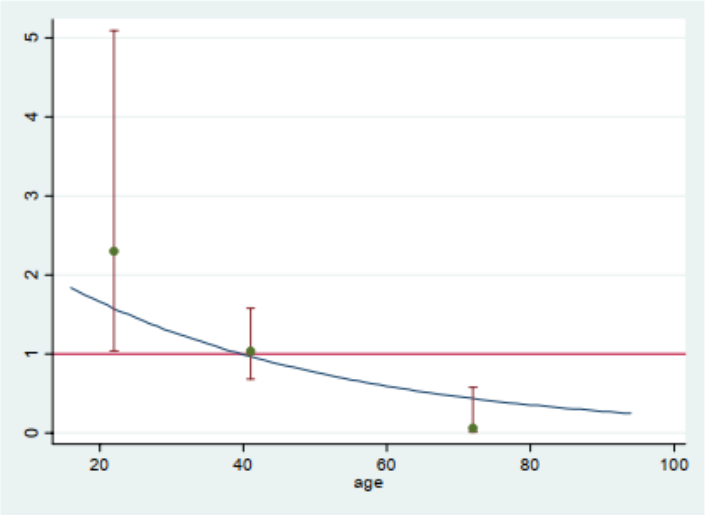


Figure 5: Suicidal Behavior Odds Ratios for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Age

A comprehensive 2005 meta-analysis that included all ages, conducted by independent researchers, found a significant increase in the odds of *suicide attempts* (odds ratio 2.28; 1.14 to 4.55, P = 0.02) for patients receiving SSRIs compared with placebo.[6] The data meant that, by treating 684 patients with an SSRI instead of placebo, one additional patient will attempt suicide.

Recently, using FDA data, independent researchers showed that the *number of suicides* was twice as high in adults (> 18 years) on the drugs than on placebo.[7,8] The odds ratio was 2.48 (1.13 to 5.44).

Thus, it is clear that the increased suicide risk has no age limit, contrary to the claim by the FDA.

The two fraudulent fluoxetine trials

Fluoxetine (Prozac) paved the way for the approval of other antidepressants in children and adolescents, and these were the two pivotal placebo-controlled trials in depression:[1,2]

Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031-7.

Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41:1205-15.

Fluoxetine was approved even though a statistical review for the FDA had noted there was not a statistically significant benefit for the drug on the primary outcome in either trial.[9,10]

Independent researchers have compared the publications with Eli Lilly's clinical study reports.[10] Neither of the peer-reviewed publications[1,2] described the suicidal events that were mentioned in the clinical study reports, X065 and HCJE, respectively.[11,12] The researchers asked Eli Lilly and Graham Emslie, the primary investigator, if they wanted to restore the trials. They did not hear from Emslie and Lilly did not believe that "any additional analyses are needed at this time."[10]

The fraud was grave, and when any serious harms of fluoxetine were mentioned, they were downplayed to the extreme. In trial X065, two of 48 patients attempted suicide on fluoxetine, but these suicide attempts were left out from the published report. Four additional patients discontinued fluoxetine because of adverse events called "minimal" in the published report, even though three of them developed manic symptoms and the fourth had a severe rash.

The clinical study report for trial X065 revealed that 32 of 48 patients on fluoxetine versus 18 of 48 patients on placebo experienced at least one adverse event (P = 0.008); 19 versus 6 experienced restlessness (P = 0.005), 9 versus 1 had nightmares (P = 0.02), and 7 versus 4 felt tense inside. Restlessness, including feeling tense inside, and nightmares, increase the risk of suicide and violence.[10] The published article did not present any such data: Only 49 words in the Results section were related to safety and they were only about discontinued patients.[1]

The efficacy analyses were seriously flawed in favour of fluoxetine and there were numerical discrepancies that amounted to mathematical impossibilities.[10] Despite this, the benefits, as measured by the psychiatrists, were so small that they lacked clinical significance, and there were no significant differences in outcomes reported by the patients.

Emslie et al. concluded in their published trial report of study X065 that "fluoxetine at 20 mg/d is safe and effective in children and adolescents with MDD" (major depressive disorder).[1] The truth is, as the independent researchers concluded for both trials, that "fluoxetine is unsafe and ineffective."[10]

The fraud was also grave for trial HCJE, in which 109 children or adolescents with depression were randomised to fluoxetine and 110 to placebo. Moreover, Eli Lilly's study report was confusingly written and there were important inconsistencies that were not explained.

Eleven patients in each group discontinued due to adverse events, six of which were for so-called nonserious psychiatric reasons on fluoxetine and one on placebo. The terms for fluoxetine were agitation, elevated mood coded as euphoria, physical aggression coded as hostility, hyperactivity coded as hyperkinesia, behavioural disinhibition coded as personality disorder, and mania. According to the narratives, these patients were more severely affected than the tables suggested. Most people would call such reactions serious even though they did not lead to hospital admission.

In total, 7 fluoxetine versus 3 placebo patients experienced psychiatric adverse events leading to discontinuation, which became 9 versus 3 patients with significant psychiatric events if two patients with akathisia on fluoxetine were added.

After 9 weeks, more patients on fluoxetine than on placebo had experienced severe adverse events. For example, 19 versus 7 patients were feeling sleepy (P = 0.01), 19 versus 9 were having trouble getting along with parents (P = 0.045), and 18 versus 7 had trouble paying attention (P = 0.02). Lilly stated that the differences were small and that the adverse events did not lead to discontinuations. However, the differences were about 10%, which means that for every 10 patients treated with fluoxetine, one was severely harmed. Nine versus 5 patients had severe problems with sitting still, which Lilly did not comment on although it could mean akathisia.

After 19 weeks, 42 patients on fluoxetine versus 28 patients on placebo had experienced nervous system events (P = 0.01). The number needed to harm was only 6, which means that by treating 6 patients with fluoxetine instead of placebo, one additional patient will be harmed.

Fluoxetine reduced the increases in height and weight over 19 weeks by 1.0 cm and 1.1 kg, respectively (P = 0.008 for both). There were no data about these important harms in the published article and no discussion of them when they were presented in the study report even though one must worry if fluoxetine also impairs brain development, which could be far worse.

Lilly concluded that "fluoxetine 20 to 60 mg/day is safe" and praised fluoxetine's benefits and lack of harms, with no mention that the children did not find fluoxetine effective or that the number needed to harm was only 6 for nervous system events and 7 for moderate or severe adverse events.

Taking the two studies together, the occurrence of adverse events definitely predisposing to violence against self or others leading to discontinuation was 11 versus 3. One of the strongest precursors for violence against self or others is akathisia. In an exploratory analysis that included akathisia and other potentially related symptoms, the independent researchers found that there were 37 versus 32 such adverse events in trial X065; 38 versus 16 in trial HCJE after 9 weeks; and 51 versus 24 after all 19 weeks.

Akathisia is a state of extreme restlessness. It literally means that you can't sit still. You may have the urge to tap your fingers, fidget, or jiggle your legs, but it can also be invisible for others, being a state of serious inner turmoil. It is a very dangerous condition that predisposes to suicide because the patients often think there is something badly wrong with them that they cannot endure. They rarely think it could be a harm of the drug they take, as they have been told that the drug is safe.

In the published trial report of study HCJE, Emslie et al. concluded that "Fluoxetine 20 mg daily appears to be well tolerated and effective for acute treatment of MDD in child and adolescent outpatients."[2]

This is blatantly false. It is also highly misleading to state that "Only one nonsolicited adverse event (headache) was reported significantly more often by fluoxetine-treated patients than by patients receiving placebo."[2]

When the FDA assessed Lilly's application for treatment of children and adolescents with fluoxetine, it included a table of discontinuations because of adverse events in X065, HCJE and HCJW, which was a trial of obsessive-compulsive disorder comparing fluoxetine 10–60 mg daily with placebo for 13 weeks in 71 versus 32 patients. There were 14 versus 3 discontinuations (P = 0.02) among the 228 versus 190 patients for reasons related to suicide and violence (suicide attempt, euphoria, manic reaction, agitation, hyperkinesia, nervousness, personality disorder, hostility, and depression).[10,13]

In these trials, there were 3 suicide attempts on fluoxetine and 1 on placebo, and another fluoxetine patient was hospitalized because of suicidality. Six patients (2.6%) on fluoxetine developed mania or hypomania versus none on placebo (P = 0.03). The FDA reviewer remarked that mania and hypomania appeared to be more common on fluoxetine in these trials than in adult clinical studies.[10,13] A table of spontaneously reported adverse events in HCJW and HCJE (9 weeks data) showed that more patients developed hyperkinesia on fluoxetine than on placebo, 12 versus 1 patients (P = 0.008). This is a serious harm, as akathisia is often miscoded as hyperkinesia.

The fraudulent paroxetine trial

Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001;40:762-72.

In this study, 93 adolescents with depression were randomised to paroxetine and 87 to placebo in an 8-week period (a third group received imipramine).

In the published report of study 329, Martin Keller et al. concluded that "Paroxetine is generally well tolerated and effective for major depression in adolescents."

It was neither of this. Independent researchers who had access to the clinical study report[14] and additional data found very different results.[15]

Keller et al. reported that 5 versus 1 patients had suicidal or self-injurious behaviours whereas the independent researchers[14] found 11 versus 1 patients (P = 0.005). Keller et al. and the clinical study report by SmithKline Beecham had mostly misreported suicide related events as "emotional lability."

The independent researchers found that 32 versus 6 patients had adverse events deemed serious by the investigators (P = 0.000006) and that 14 versus 6 patients withdrew from the trial because of adverse events. In contrast, Keller et al. reported that only 9 versus 6 patients withdrew from the trial because of adverse events.

The independent researchers found that "The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any prespecified primary or secondary efficacy outcome." But changes were made post-hoc to some of the outcomes, both before and after breaking the blind, without being stated in any of the protocol amendments or in the published article, whereby they became statistically significant. This is fraud.

Consequences of the fraudulent trial reports

The consequences of the fraudulent trials are huge, and the fraud is not limited to trials of fluoxetine and paroxetine.[5] They just happened to be the drugs where the fraud has been most closely examined.

A systematic review of placebo-controlled antidepressant trials (all ages) based on clinical study reports also found highly disturbing data.[16] For children and adolescents, the odds ratios were 2.39 (1.31 to 4.33) for suicidality, 2.79 (1.62 to 4.81) for aggression, and 2.15 (0.48 to 9.65) for akathisia (which was underreported because of the coding dictionaries used). Four deaths were misreported by the company, in all cases favouring the active drug.

Patient narratives were only available for serious events and for aggression. They included homicidal threat, homicidal ideation, assault, sexual molestation, and a threat to take a gun to school (all five participants receiving sertraline), damage to property, punching household items, aggressive assault, verbally abusive and aggressive threats (all five participants receiving paroxetine), and belligerence (fluoxetine).[16] Such harms are not likely to ever appear in published trial reports.

Clinicians get the knowledge they use to guide their practice from the peer reviewed literature, from guidelines based on journal publications and not on clinical study reports, and from drug salespeople that often hand over reprints of fraudulent trial reports to them. It is therefore not surprising that antidepressants are used for almost everything, also for children and young people, because clinicians think they are safe and effective.

This is a fatal mistake. Many children and young people who were driven to suicide by the harms of the antidepressant they took did not even have a condition that justified the prescription, e.g. their problem could be insomnia, stress at work, anxiety before a school exam, or break-up with a girlfriend.[5]

It is characteristic for antidepressant induced suicide that people choose highly violent means, e.g. hanging or shooting. They feel so terrible because of the harms of the pills that they want to be sure that they will end their lives. In contrast, people who attempt suicide because of depression often use other means, e.g. an overdose of pills, which gives them a chance of surviving and is usually a cry for help.

All the 10 people who have signed this letter because they lost a child or a spouse due to antidepressant induced suicide have experienced that the suicide was accomplished by violent means: hanging, shooting, stabbing, or jumping in front of a train (see below). Most of the tragic stories appear in a book.[55 (page 79 onwards)]

We call on you as responsible editors to retract the fraudulent papers without delay. We have attached copies of the 16 references we mention in this letter or have provided links to them (see the reference list below).

We are looking forward to your reply.

Yours sincerely

Peter C. Gøtzsche, Professor Emeritus, Institute for Scientific Freedom, Copenhagen

Kim Witczak, Minnesota, Consumer Representative at the FDA Psychopharmacological Advisory Group meetings, lost her 37-year old husband to drug induced suicide. He was prescribed sertraline because of insomnia and hanged himself.

Denis Terrida, Denmark, lost his 20-year old son to drug induced suicide. He was prescribed sertraline because he did not feel well psychologically and hanged himself.

Maria Bradshaw, New Zealand, lost her 17-year old son to drug induced suicide. He was prescribed fluoxetine because he was stressed due to a breakup with a girlfriend and hanged himself.

Stephanie McGill Lynch, Ireland, lost her 14-year old son to drug induced suicide. He was prescribed fluoxetine for anxiety and shot himself.

Leonie Fennell, Ireland, lost her 22-year old son to drug induced suicide. He was prescribed citalopram after he broke up with his girlfriend and stabbed himself and his ex-girlfriend’s new boyfriend to death.

Wendy Dolin, Illinois, lost her 57-year old husband to drug induced suicide. He was prescribed paroxetine because of anxiety at work and threw himself in front of a train.

Mathy Downing, Maryland, lost her 12-year old daughter to drug induced suicide. She was prescribed paroxetine because of school anxiety and hanged herself.

Maryellen Winter, New York, lost her 22-year old daughter to drug induced suicide. She was prescribed paroxetine because of insomnia and hanged herself. Her mother gave testimony at the FDA hearing on 13 Dec 2006: https://www.youtube.com/watch?v=_4JXyEJaGX4).

Cheryl Miller, Kansas, lost her 13-year old son to suicide. He was prescribed sertraline because he was unhappy and hanged himself.

Kristina Kaiser, Florida, lost her 19-year old daughter to drug induced suicide. She was prescribed sertraline for "OCD like tendencies" and died from a self-sustained injury two days after a dose increase that caused akathisia.

Signatures:

Peter C Gøtzsche

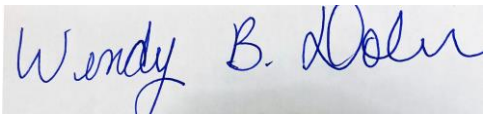
Kim Witczak

Denis Terrida

Maria Bradshaw

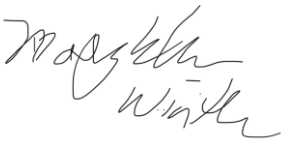
Stephanie McGill Lynch

Leonie Fennell



Wendy Dolin

Mathy Downing



Maryellen Winter

Cheryl Miller

Kristina Kaiser

References

1 Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031-7.

2 Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41:1205-15.

3 Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001;40:762-72.

4 Laughren TP. Overview for December 13 Meeting of Psychopharmacologic Drugs Advisory Committee (PDAC). 2006 Nov 16. www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf (accessed 22 October 2012). When using the link in 2023, this message appeared: "Access Denied. You don't have permission to access 'http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf' on this server."

5 Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

6 Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005;330:396.

7 Hengartner MP, Plöderl M. Newer-generation antidepressants and suicide risk in randomized controlled trials: a re-analysis of the FDA database. Psychother Psychosom 2019;88:247-8.

8 Hengartner MP, Plöderl M. Reply to the Letter to the Editor: "Newer-Generation Antidepressants and Suicide Risk: Thoughts on Hengartner and Plöderl's ReAnalysis." Psychother Psychosom 2019;88:373-4.

9 Shen, Y-L. Application number: 18-936/SE5-064. Statistical review. FDA 2001; 20 July.

10 Gøtzsche PC, Healy D. Restoring the two pivotal fluoxetine trials in children and adolescents with depression. Int J Risk Saf Med 2022;33:385-408.

11 Eli Lilly and Company. Protocol B1Y-MC-X065. Clinical study main report: Fluoxetine versus placebo in the acute treatment of major depressive disorder in children and adolescents. 2000.

12 Eli Lilly and Company. Protocol B1Y-MC-HCJE. Clinical study report: Fluoxetine versus placebo in childhood/adolescent depression. 2000.

13 Mosholder AD. Application number: 18-936/SE5-064. Medical review. FDA 2001.

14 SmithKline Beecham. A multi-center, double-blind, placebo controlled study of paroxetine and imipramine in adolescents with unipolar major depression – acute phase, Final clinical report.

15 Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Restoring Study 329: Efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 2015;351:h4320.

16 Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016;352:i65.