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RESEARCH

Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration

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ABSTRACT

Objective To examine the risk of suicidal behaviour within clinical trials of antidepressants in adults.

Design Meta-analysis of 372 double blind randomised placebo controlled trials.

Setting Drug development programmes for any indication in adults.

Participants 99 231 adults assigned to antidepressants or placebo. Median age was 42 and 63.1% were women. Indications for treatment were major depression (45.6%), other depression (4.6%), other psychiatric disorders (27.6%), and non-psychiatric disorders (22.2%).

Main outcome measures Suicidal behaviour (completed suicide, attempted suicide, or preparatory acts) and ideation.

Results For participants with non-psychiatric indications, suicidal behaviour and ideation were extremely rare. For those with psychiatric indications, risk was associated with age. For suicidal behaviour or ideation and for suicidal behaviour only, the respective odds ratios were 1.62 (95% confidence interval 0.97 to 2.71) and 2.30 (1.04 to 5.09) for participants aged <25, 0.79 (0.64 to 0.98) and 0.87 (0.58 to 1.29) for those aged 25-64, and 0.37 (0.18 to 0.76) and 0.06 (0.01 to 0.58) for those aged ≥65. When age was modelled as a continuous variable, the odds ratio for suicidal behaviour or ideation declined at a rate of 2.6% per year of age (−3.9% to −1.3%, P=0.0001) and the odds ratio for suicidal behaviour declined at a rate of 4.6% per year of age (−7.4% to −1.8%, P=0.001).

Conclusions Risk of suicidality associated with use of antidepressants is strongly age dependent. Compared with placebo, the increased risk for suicidality and suicidal behaviour among adults under 25 approaches that seen in children and adolescents. The net effect seems to be neutral on suicidal behaviour but possibly protective for suicidal ideation in adults aged 25-64 and to reduce the risk of both suicidality and suicidal behaviour in those aged ≥65.

INTRODUCTION

Some patients being treated for depression and other psychiatric illnesses experience suicidal thoughts and actions (suicidality). There is a longstanding belief that antidepressants might have an early "activating effect" that gives depressed patients the energy to follow through on suicidal impulses before the mood improvement also provided by antidepressant treatment takes effect. Concern about the possibility of an increased risk of suicide with fluoxetine led to a meeting of the US Food and Drug Administration (FDA) psychopharmacologic drugs advisory committee in 1991. The committee concluded that there was no clear evidence of an increased risk. Labelling at that time included a general statement about the risk of suicide associated with depression and did not directly suggest a causative role for antidepressants.

Over the next decade, additional data were accumulated as applications for newer antidepressants were reviewed and the drugs were marketed. Looking at adult data from FDA reviews, Khan et al reported that the risk of completed suicide was the same for drugs and placebo.[1] Storosum et al analysed attempted suicides from adult data available from the medicines evaluation board of the Netherlands and reached the same conclusion.[2] An independent FDA analysis of completed suicides from placebo controlled, short term trials of antidepressants in adults also found no drug related increase,[3] but the strength of this conclusion was tempered by the low number of completed suicides in the trials.

Analysis of data from several paediatric trials on paroxetine in 2003 raised a particular concern that antidepressant drug treatment might have led to attempted suicide and ideation in children and adolescents. The FDA asked all manufacturers who had sponsored trials of antidepressants in children and adolescents to search for reports of suicidal thinking or behaviour during those trials and submit them to the agency. These reports were the basis of an analysis

presented to a joint meeting of two FDA advisory committees in 2004.[4] It showed a relative risk for suicidal behaviour or ideation of 1.95 (95% confidence interval 1.28 to 2.98) for those treated with antidepressants compared with those given placebo. The committees recommended that the FDA add a boxed warning to antidepressant labelling (implemented early in 2005) and review clinical trials of antidepressants in adults to look for similar effects. Two previous published meta-analyses in adults did not have access to primary data, could not validate the identification and classification of suicidal events, and had limited means to establish both the appropriateness of the included trials and the inclusion of all relevant trials.[5,6] In addition, the outcomes considered were not comparable with those used in the FDA study of paediatric trials. We carried out a review to respond to the committees' request and address limitations of the published meta-analyses.

METHODS

Data collection

The FDA asked eight industry sponsors of 12 marketed antidepressant products (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluoxetine/olanzapine (ultimately excluded from the analysis), fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine) for datasets from all double blind randomised placebo controlled trials of antidepressant in adults for any indication.

The variables included in these datasets provided detailed information about individual participants. Sponsors' dataset submissions were received by the FDA between September 2005 and September 2006 as electronic files (in SAS transport file format).

Data were requested from completed, double blind randomised placebo controlled trials with at least 20 participants in each treatment arm. Trials limited to known drug responders, such as those using randomised withdrawal designs, were not included; such studies do not examine the effects of initiating treatment and would eliminate as non-responders those who had shown suicidality during drug treatment.

We asked sponsors to provide a list of all known trials, indicating which trials the sponsor planned to include and which they intended to exclude from the dataset and why. We then provided feedback to the sponsors on which trials should be included in the final dataset. Sponsors summarised the characteristics of the trials included in the datasets in the form of two tables: one providing the dose, duration, and number of participants per trial, and the other providing the trial exclusion criteria.

Other than dataset formats, instructions for identifying and classifying events possibly related to suicidality (suicidal thoughts and actions) and the event classification process, we did not specify who or how companies should retrieve or compile the information we requested. Each company has its own system for archiving and maintaining its records of clinical studies. They are in the best position to judge the optimal approach to completing these tasks. Each company designated a person to serve as the main contact with the FDA.

Adverse events in these trials were solicited by general inquiry and recorded in case report forms. Following the approach used in the paediatric study,[4] sponsors were asked to search their electronic databases for adverse events reported during the double blind phase of treatment for terms related to suicidality. Because it was difficult to determine whether events represented a change in condition or resulted from a pre-existing condition, all events reported during the double blind phase were included. Events that occurred more than a day after the randomised treatment stopped were excluded.

The data request letter asked sponsors to search clinical trial databases for preferred terms, verbatim terms, and any comment fields for the following text strings: "accident-", "attempt", "burn", "cut", "drown", "gas", "gun", "hang", "hung", "immolat", "injur-", "jump", "monoxide", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", "firearm". All events identified by this search were considered as possibly related to suicidality, unless they were identified as "false positive" results: events that included any of these text strings but were not related to suicidality. For example, "epigastric pain" would be identified in the search for the text string "gas." Sponsors submitted listings of the events they classified as "false positives," which were reviewed by FDA staff.

The datasets included 406 clinical trials with 103 491 participants. Six trials were duplicated in the submissions. We excluded 28 other trials: 23 because at least one trial arm contained fewer than 20 participants, three because data at the patient level were not available, and two because the study drug was a combined antidepressant/antipsychotic. We also excluded participants assigned to a non-antidepressant active control drug (608), leaving a total of 372 trials with 99 231 participants (fig 1). Most of the studies were unpublished; those that had been published in some form seldom contained information concerning suicidality in the publication. None of the studies was included in the previous study of paediatric trials.

Determination of suicidality outcomes

Sponsors prepared case narratives for each event possibly related to suicidality (suicidal thoughts and actions). Details that might bias classification (such as treatment assignment) were removed. Because of the large number of participants, the sponsors and not the FDA adjudicated events. Adjudicators, who were blinded to treatment assignment, classified events using the approach of Posner et al.[7] Events were classified into seven mutually exclusive categories: 1 completed suicide, 2 suicide attempt, 3 preparatory acts towards imminent suicidal behaviour, 4 suicidal ideation, 5 self injurious behaviour, intent unknown, 6 not enough information (fatal), and 7 not enough

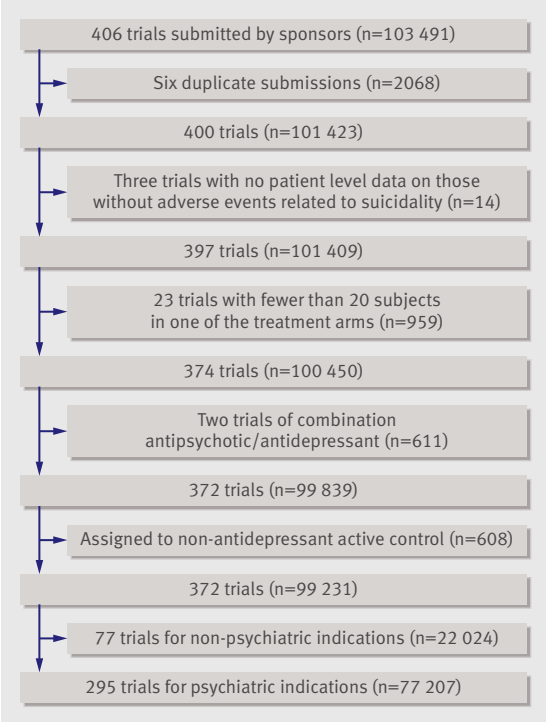

Fig 1 | **Flow diagram of exclusions of trials and participants (numbers shown in parentheses)**

information (non-fatal). For participants with multiple events, we coded only the most severe event (for example, completed suicide would be coded rather than suicide attempt if both had occurred).

Three individuals with appropriate training and expertise independently rated events. Sponsors engaged outside contractors experienced in the method of Posner et al,[7] either to conduct the rating process or to train the sponsor's staff. If the three raters were not unanimous in their ratings, a discussion among the raters, led by a fourth rater, was conducted with the goal of achieving consensus. If consensus was not achieved, the event was rated as indeterminate (category 6 or 7).

Statistical analysis

The primary outcome was defined as suicidal ideation or worse (categories 1, 2, 3, or 4). This corresponded to the primary outcome (definitive suicidal behaviour/ideation) used in the FDA's paediatric analysis of suicidality. The second outcome variable, considered in parallel with the primary outcome, was preparatory actions or worse (categories 1, 2, or 3), also called suicidal behaviour. We looked at ideation alone for the sake of comparison but did not consider it a clinically important outcome because the category excludes both those who had neither suicidal ideation nor behaviour and those who had both. Because of the previous finding of increased suicidality with antidepressant use in children and adolescents, we considered findings within the general outcomes of suicidal ideation or worse and suicidal behaviour or worse that would be consistent with this observation in a set order. The primary hypothesis for each outcome was that the outcome would be increased among all adults using antidepressants. The principal secondary hypothesis, contingent on rejection of the primary hypothesis, was that the subpopulation of adults most similar to children and adolescents—that is, young adults (defined as age <25)—would show an increased risk. If this second hypothesis was confirmed, we would then consider the possibility of an increased risk in the next youngest 10 year group (age 25-34), and so forth.

We used conditional logistic regression to calculate odds ratios and obtained risk differences with population averaged general estimating equations. These methods were chosen for computational speed and ease of inclusion of covariates. The insensitivity of the results to the method was supported by obtaining similar results for the principal analyses with other techniques: exact methods, Mantel-Haenszel, Bayesian, and unconditional and random effects logistic regression.[8] All analyses were conditioned or stratified by study. To examine trial heterogeneity, we added treatment by trial interaction terms to the model. Heterogeneity of effect by drug and drug class was similarly modelled. We used a random effects logistic regression model to model age and age-treatment interaction as continuous variables in a post hoc analysis. Analyses were performed with Stata version 9.2 and SAS version 9.1.

Subgroup analyses were performed based on demographics, characteristics at the trial level, indication, and drug class. As we were particularly interested in age because of the association of suicidality with antidepressant use in the paediatric population, we performed analyses using age and the interaction of age with treatment as both categorical and continuous variables.

To obtain results that could be directly compared with two published meta-analyses of suicidality in clinical trials of selective serotonin reuptake inhibitors (SSRIs),[5,6] we compared odds ratios for SSRI with placebo for completed suicide (outcome 1), non-fatal self harm (outcomes 2 and 5), and suicidal ideation alone (outcome 4), and, for SSRIs compared with tricyclics, for any suicide attempt (outcomes 1 and 2).

We classified treatment indications into one of five indication groups by FDA physicians: major depressive disorder, other depressive disorders, other psychiatric disorders, other behavioural disorders, and non-behavioural disorders. We divided the 18 antidepressant drugs used as either primary drugs or active controls in adult trials into five classes: selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), other modern antidepressants, tricyclic antidepressants, and other antidepressants.

RESULTS

Characteristics of the data

Table 1 summarises the demographic characteristics of the study population. The total duration of

Table 1 | Demographic data for 99 231 people included in randomised placebo controlled trials on antidepressants

	Percentage*
Age (years):	
Mean	43.1
Median (range)	42 (15-99)
<25	8.0
≥65	8.6
Sex:	
Female	63.1
Male	36.9
Ethnicity:	
White	86.9
Black	5.2
Hispanic	3.5
Asian	2.7
Other	1.6
Location:	
North America	75.5
Other countries	24.5
Indication class:	
Major depression	45.6
Other depression	4.6
Other psychiatric	27.6
Behavioural	13.5
Other	8.7

*Except where stated otherwise.

observation was 15 505 person years. Table 2 shows the numbers of participants by drug, drug class, and treatment assignment. Table 3 shows the incidence of suicidality by indication group. There were eight reported completed suicides, 134 reported suicide attempts, 10 reports of preparations without attempted suicide, and 378 reported suicidal ideation alone—that is, without any action. The incidence rates for suicidality in those with major depression were higher than in the other indication groups; incidence rates for other depressive disorders and psychiatric disorders other than depression were about two thirds of that for major depression. The rates for non-psychiatric disorders were much lower than for psychiatric disorders and consisted almost entirely of suicidal ideation alone. For the psychiatric categories, the ratio of participants with ideation only to participants who attempted suicide was about three to one (360/133). In the non-psychiatric categories there were 18 cases of ideation alone but only one suicide attempt.

Estimates of risk of suicidality associated with antidepressant treatment

Table 4 shows the estimated odds ratios and risk differences for suicidal ideation or worse associated with assignment to antidepressant drug treatment compared with placebo. For the entire dataset, the odds ratio was 0.85 (95% confidence interval 0.71 to 1.02). The estimated odds ratio for preparatory acts or worse was 1.12 (0.79 to 1.58). The odds ratio for completed suicide (2.13) was higher for those treated with an antidepressant, but this was based on just eight events and was not significant (0.41 to 10.99).

Table 4 also compares risk of suicidality by indication. The psychiatric indication categories seem remarkably similar, while the non-psychiatric categories seem similar to each other but distinct from the psychiatric categories. The difference between the psychiatric diagnoses and the non-psychiatric diagnoses, however, was not significant (P=0.25). As there were few events in the non-psychiatric categories, an estimate combining observations across all categories would be largely determined by the events in psychiatric trials; it might be misleadingly applied to people with non-psychiatric indications. Therefore, we have limited further analyses presented to the 77 207 participants in 295 clinical trials for psychiatric indications.

Table 5 shows the odds ratios and risk differences for suicidality for antidepressant treatment in psychiatric disorders by drug and drug class. For the entire population with psychiatric disorders, there was a decrease in suicidality with treatment. Other statistical techniques showed nearly identical results. Statistical tests for differences in effect among drugs and drug classes had negative results, with the exception of some indication of differences among SSRIs. There was little difference between older and newer drugs. The odds ratios for suicidal behaviour were slightly higher than those observed for suicidality.

Estimates of heterogeneity in treatment effect among trials and of interaction of treatment effect with status of a drug as test drug or active control, trial location, sex, and ethnicity were all non-significant (P>0.35).

Table 2 | Numbers of participants by drug, drug class, and treatment assignment

Drug	Primary	Active control	Placebo
Selective serotonin reuptake inhibitor:			
Citalopram	1928	733	1371
Escitalopram	2567	563	2604
Fluoxetine	9070	2418	7645
Fluvoxamine	2187	0	1828
Paroxetine	8728	1223	7005
Sertraline	5821	1129	5589
Duloxetine	6361	0	4172
Venlafaxine	5693	129	4054
Other modern antidepressants:			
Bupropion	6018	0	3887
Mirtazapine	1268	0	726
Nefazodone	3319	0	2173
Tricyclic antidepressants:			
Amitriptyline	0	625	627
Clomipramine	0	632	617
Desipramine	0	315	298
Dosulepin	0	106	95
Imipramine	0	2345	2304
Other antidepressants:			
Mianserin	0	28	28
Trazodone	0	121	125
All drugs	52 960	10 367	35 904

Table 3 | Incidence of suicidal behaviour or ideation by indication group. Figures are numbers (percentages) of participants

	Major depression	Other depression	Other psychiatric	Behavioural	All other	Total
Completed suicide	6 (0.01)	0	2 (0.01)	0	0	8 (0.01)
Attempted, not completed	90 (0.20)	7 (0.15)	36 (0.13)	1 (0.01)	0	134 (0.14)
Preparation, no attempt	7 (0.02)	1 (0.02)	2 (0.01)	0	0	10 (0.01)
Ideation alone	238 (0.53)	14 (0.30)	108 (0.39)	8 (0.06)	10 (0.12)	378 (0.38)
Total	341 (0.76)	22 (0.47)	148 (0.54)	9 (0.07)	10 (0.12)	530 (0.54)

Table 6 and figure 2 show the risks by age for suicidality associated with assignment to antidepressant treatment for adults with psychiatric disorders. The most striking observation is the higher odds ratio and risk difference with antidepressant treatment than with placebo in those aged under 25 but lower odds ratio and risk difference in those aged 25 or older. There might also be a further distinction between a modest protective effect of antidepressants in people aged 25-64 and a stronger protective effect in those aged 65 and older. When we modelled age as a continuous variable, the odds ratio declined at a rate of 2.6% per year of age (−3.9% to −1.3%, P=0.001).

Table 6 also shows risks by age for suicidal ideation and suicidal behaviour. The decline in odds ratio and risk difference with age for suicidal ideation alone was relatively slight; the differences between major age categories were not significant (table 7), except when we modelled age as a continuous variable (change in odds ratio −1.8% per year of age, −3.3% to −0.4%, P=0.014, table 8). For suicidal behaviour, with a smaller number of events, the decline in odds ratios with age seems steeper and the differences between age categories were more significant. When we modelled age as a continuous variable, the odds ratio declined at a rate of 4.6% per year of age (−7.4% to −1.8%, P=0.001). Table 9 shows the odds ratios and risk differences for suicidality, suicidal ideation alone, and suicidal behaviour broken down by age and indication category. A pattern of increase in both odds ratio and risk difference with decreasing age is generally apparent across all outcomes and diagnostic categories. The largest increase in risk associated with antidepressants seems to have been in those aged under 25 with psychiatric disorders other than depression.

DISCUSSION

In contrast with the results of the review of paediatric studies on suicide and antidepressants by the US Food and Drug Administration (FDA),[4] pooled estimates for the adult population did not show an increased risk of suicidality. When we analysed results by age, however, we found an increased risk among adults aged under 25 that approached the risk seen in children and adolescents. The net effect seems moderately protective for adults aged 25-64 and more strongly protective in those aged 65 and older. This age related gradient seemed steeper for suicidal behaviour than for ideation alone.

Because the relation between antidepressant use and suicidality seems to be age related, the overall result is probably a consequence of the particular age distribution of the participants in the study population. This population was not chosen to be representative of the age distribution of antidepressant users. If the population had skewed younger, the overall result would probably have shown a higher risk; if the population had skewed older, the overall risk would probably have been lower. The overall estimates are therefore not generalisable.

Strengths and limitations of this study

Our study has several features not present in most other systematic reviews. We were able to apply a uniform approach to the detection of possible suicide related events across hundreds of studies and used a validated method with proved inter-rater reliability for classification of events.

This study differs in important ways from most meta-analyses, which rely on the published results of analyses performed in individual studies and combines

Table 4 | Suicidality risk for active drug relative to placebo (ideation or worse) in all adults by indication

	Drug		Placebo			
Indication category	Events	Participants	Events	Participants	Odds ratio (95% CI), P value	Risk difference/1000 (95% CI), P value
All indications	326	63 327	204	35 904	0.85 (0.71 to 1.02), 0.08	−0.87 (−1.89 to 0.15), 0.10
Psychiatric indications:						
All	314	50 043	197	27 164	0.83 (0.69 to 1.00), 0.05	−1.28 (−2.57 to 0.00), 0.05
Major depression	218	30 485	123	14 728	0.85 (0.67 to 1.07), 0.16	−1.42 (−3.23 to 0.40), 0.12
Other depression	13	2744	9	1863	0.90 (0.38 to 2.14), 0.81	−0.15 (−4.40 to 4.11), 0.95
Other	83	16 814	65	10 573	0.79 (0.56 to 1.11), 0.17	−1.37 (−3.33 to 0.59), 0.17
Non-psychiatric indications	12	13 284	7	8740	1.47 (0.57 to 3.79), 0.42	0.28 (−0.50 to 1.05), 0.48
Behavioural indications	6	8144	3	5218	1.43 (0.35 to 5.86), 0.62	0.16 (−0.72 to 1.03), 0.72
Other indications	6	5140	4	3522	1.51 (0.42 to 5.40), 0.53	0.38 (−0.96 to 1.73), 0.58

Table 5 | Suicidality risk for active drug relative to placebo (ideation or worse) in adults with psychiatric disorders by drug and drug class

	Drug		Placebo			
Drug class	Events	Participants	Events	Participants	Odds ratio (95% CI), P value	Risk difference/1000 (95% CI), P value
All drugs	314	50 043	197	27 164	0.83 (0.69 to 1.00), 0.05	−1.28 (−2.57 to 0.00), 0.05
Selective serotonin reuptake inhibitor:						
All	205	31 440	141	21 225	0.86 (0.69 to 1.06), 0.16	−0.60 (−2.07 to 0.88), 0.43
Citalopram	24	2 661	7	1 371	2.11 (0.90 to 4.94), 0.09	4.05 (−1.38 to 9.49), 0.14
Escitalopram	10	3 130	5	2 604	2.44 (0.90 to 6.63), 0.08	1.27 (−1.38 to 3.93), 0.35
Fluoxetine	81	7 180	67	4 814	0.71 (0.52 to 0.99), 0.04	−3.39 (−7.61 to 0.82), 0.11
Fluvoxamine	22	2 187	13	1 828	1.25 (0.66 to 2.39), 0.49	3.13 (−2.80 to 9.06), 0.30
Paroxetine	50	9 919	29	6 972	0.93 (0.62 to 1.42), 0.75	0.50 (−1.56 to 2.55), 0.64
Sertraline	18	6 363	28	5 081	0.51 (0.29 to 0.91), 0.02	−2.50 (−4.99 to −0.01), 0.05
Serotonin-noradrenaline reuptake inhibitor:						
All	54	7 920	48	5 364	0.81 (0.56 to 1.19), 0.28	−2.45 (−5.69 to 0.80), 0.14
Duloxetine	25	2 327	18	1 460	0.88 (0.47 to 1.63), 0.68	−2.23 (−9.11 to 4.65), 0.52
Venlafaxine	29	5 593	30	3 904	0.71 (0.44 to 1.16), 0.17	−2.55 (−6.02 to 0.92), 0.15
Other modern antidepressants:						
All	27	6 511	24	4 225	0.83 (0.49 to 1.41), 0.49	−1.18 (−4.09 to 1.74), 0.43
Bupropion	7	2 659	4	1 800	1.35 (0.45 to 4.06), 0.59	−0.50 (−3.15 to 2.14), 0.71
Mirtazapine	8	1 016	6	644	0.97 (0.34 to 2.78), 0.96	−0.02 (−9.14 to 9.11), 1.00
Nefazodone	12	2 836	14	1 781	0.65 (0.30 to 1.41), 0.28	−3.38 (−8.36 to 1.61), 0.18
Tricyclic antidepressants:						
All	27	4 023	39	3 941	0.71 (0.45 to 1.12), 0.14	−3.98 (−8.06 to 0.10), 0.06
Amitriptyline	0	625	1	627	0 (0 to ∞), 0.99	−1.59 (−4.72 to 1.54), 0.32
Clomipramine	5	632	12	617	0.49 (0.18 to 1.34), 0.17	−11.48 (−24.4 to 1.41), 0.08
Desipramine	1	315	2	298	0.63 (0.06 to 6.25), 0.69	−3.56 (−14.76 to 7.64), 0.53
Dosulepin	0	106	1	95	0 (0 to ∞), 0.99	−10.53 (−31.0 to 1.00), 0.32
Imipramine	21	2 345	23	2 304	0.88 (0.50 to 1.53), 0.64	−2.38 (−8.19 to 3.43), 0.42
Other antidepressants:						
All	1	149	2	153	0.61 (0.06 to 5.95), 0.67	−6.58 (−29.6 to 16.4), 0.58
Mianserin	1	28	1	28	1.00 (0.06 to 16.8), 1.00	0 (−97.2 to 97.2), 1.00
Trazodone	0	121	1	125	0 (0 to ∞), 0.99	−9.03 (−23.3 to 5.27), 0.22

them into a single estimate of effect. Our study, in contrast, analysed the primary data from adverse event reports on individual subjects to identify suicidality events occurring within a collection of clinical trials. (Some of the trials included in the analysis were the basis of articles published in peer reviewed journals but the question of suicidality was not considered in any detail by the authors or reviewers.) We analysed the data as primary data even though we were not directly involved in the data collection. We believe that our approach provided a high level of assurance as to the completeness and accuracy of the data. Federal law requires that any research study of a drug that has not been licensed for sale in the US and that involves humans in the US must be reviewed in advance by the FDA. This requirement is extended to drugs already licensed for sale if the study in question is intended to support commercial use, such as a possible application for a new indication or changing information in the drug label about safety or efficacy. This means that the FDA has a record of virtually every company supported clinical trial performed on people in the US as well as reports of the results of those studies. In addition, any study performed entirely outside the US that provides information used in a licensing application will also be reported. In many cases the study reports included the original datasets and adverse event reports. This provided us with an excellent reference source with which to confirm the accuracy and completeness of the submissions that were specifically requested for our study. Furthermore, FDA staff are experts on the clinical development programmes for these drugs and were already familiar

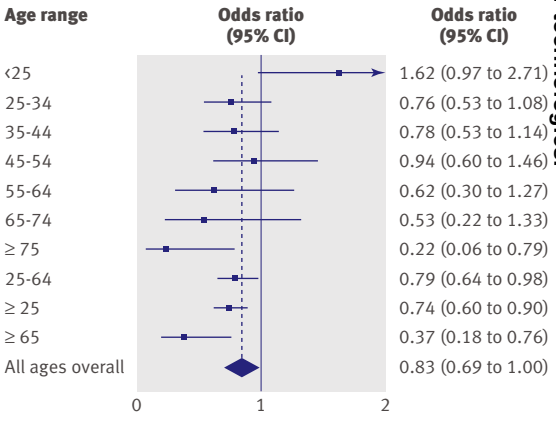

Fig 2 | Odds of suicidality (ideation or worse) for active drug relative to placebo by age in adults with psychiatric disorders

with many of these studies. As part of the submissions for our study, companies submitted tables of included and excluded studies, as well as summary descriptions of the included studies. The information in these tables was reviewed by FDA staff for inconsistencies with what was known from information provided in the past. In addition, as part of the process of cleaning the datasets, we compared the information in the datasets with what was described in the summary tables for consistency in terms of number of participants per arm, demographic information, drugs used, and timing and number of adverse events.

The main limitation of our study is its inability to address all the patients and circumstances with an indication for antidepressants. Patients at highest risk for suicide are extremely unlikely to be entered into placebo controlled trials. Moreover, most of the studies included in this analysis involved the initial treatment of an acute condition over eight to 10 weeks of observation. It would not be surprising if epidemiological studies (or long term randomised trials) showed a different picture. Patients receiving antidepressants for maintenance of a chronic condition or prevention of relapse, who constitute much of the population taking these drugs, might not be affected in the same way as acutely treated patients; maintenance treatment with antidepressants could, for example, reduce suicides over the longer term. This study can also do little to resolve whether antidepressants affect the risk of death by suicide; even in a population of tens of thousands, there was only a handful of cases.

Another potential problem in this study is the sparseness of the data. Many trials had only one event or no events at all. This can potentially cause important problems for statistical techniques, particularly when the treatment arms are unbalanced.[9] Our results, however, were highly robust and largely unaffected by choice of statistical technique. In particular, the most interesting finding—the continuous reduction in risk associated with treatment with age—has such strong significance that it would be unlikely to have been an artefact of problems related to sparseness of data.

Table 6 | Suicidality risk by age for active drug relative to placebo in adults with psychiatric disorders

	Drug		Placebo			
Age range	Events	Participants	Events	Participants	Odds ratio (95% CI), P value	Risk difference/1000 (95% CI), P value
Ideation or worse						
<25	64	4780	21	2621	1.62 (0.97 to 2.71), 0.07	5.34 (0.61 to 10.1), 0.03
≥25	250	45 263	176	24 543	0.74 (0.60 to 0.90), 0.003	−1.96 (−3.28 to −0.64), 0.004
25-64	238	41 331	152	22 126	0.79 (0.64 to 0.98), 0.03	−1.48 (−2.84 to −0.11), 0.03
25-34	85	12 479	54	6813	0.76 (0.53 to 1.08), 0.13	−1.61 (−4.23 to 1.02), 0.23
35-44	74	14 002	48	7564	0.78 (0.53 to 1.14), 0.2	−1.33 (−3.52 to 0.86), 0.24
45-54	60	9805	34	5074	0.94 (0.60 to 1.46), 0.78	−0.64 (−3.43 to 2.15), 0.65
55-64	19	5045	16	2675	0.62 (0.30 to 1.27), 0.19	−1.94 (−5.18 to 1.30), 0.24
≥65	12	3907	24	2397	0.37 (0.18 to 0.76), 0.007	−6.34 (−10.8 to −1.91), 0.005
65-74	9	2663	12	1595	0.53 (0.22 to 1.33), 0.18	−3.87 (−8.69 to 0.95), 0.12
≥75	3	1244	12	790	0.22 (0.06 to 0.79), 0.02	−12.4 (−21.7 to −3.16), 0.01
Ideation alone						
<25	32	4780	13	2621	1.19 (0.61 to 2.35), 0.61	1.71 (−1.84 to 5.26), 0.34
≥25	180	45 263	135	24 543	0.70 (0.55 to 0.88), 0.003	−1.73 (−2.86 to −0.59), 0.003
25-64	169	41 331	118	22 126	0.72 (0.56 to 0.92), 0.01	−1.53 (−2.71 to −0.35), 0.01
25-34	58	12 479	37	6813	0.73 (0.48 to 1.13), 0.16	−1.16 (−3.31 to 0.99), 0.29
35-44	53	14 002	37	7564	0.74 (0.47 to 1.16), 0.19	−1.31 (−3.20 to 0.59), 0.18
45-54	44	9805	30	5074	0.77 (0.47 to 1.25), 0.29	−1.5 (−4.05 to 1.05), 0.25
55-64	14	5045	14	2675	0.56 (0.25 to 1.27), 0.16	−2.01 (−4.90 to 0.87), 0.17
≥65	11	3907	17	2397	0.53 (0.25 to 1.16), 0.11	−3.32 (−6.86 to 0.22), 0.07
65-74	8	2663	8	1595	0.83 (0.30 to 2.28), 0.72	−1.49 (−5.36 to 2.39), 0.45
≥75	3	1244	9	790	0.29 (0.08 to 1.11), 0.07	−8.54 (−16.6 to −0.53), 0.04
Suicidal behaviour						
<25	32	4780	8	2621	2.30 (1.04 to 5.09), 0.04	3.64 (0.51 to 6.77), 0.02
≥25	70	45 263	41	24 543	0.87 (0.58 to 1.29), 0.48	−0.19 (−0.84 to 0.46), 0.57
25-64	69	41 331	34	22 126	1.03 (0.68 to 1.58), 0.88	0.09 (−0.58 to 0.76), 0.8
25-34	27	12 479	17	6813	0.81 (0.43 to 1.52), 0.53	−0.36 (−1.82 to 1.10), 0.63
35-44	21	14 002	11	7564	0.89 (0.42 to 1.87), 0.75	−0.00 (−1.10 to 1.10), 1.00
45-54	16	9805	4	5074	2.29 (0.73 to 7.14), 0.15	0.84 (−0.27 to 1.96), 0.14
55-64	5	5045	2	2675	0.89 (0.17 to 4.73), 0.89	0.20 (−1.25 to 1.66), 0.78
≥65	1	3907	7	2397	0.06 (0.01 to 0.58), 0.01	−2.85 (−5.23 to −0.48), 0.02
65-74	1	2663	4	1595	0.09 (0.01 to 0.95), 0.04	−2.18 (−4.80 to 0.43), 0.10
≥75	0	1244	3	790	0 (0 to ∞), 1.00	−3.71 (−7.04 to −0.37), 0.03

Table 7 | Comparison of age specific risks for drug effect on suicidality

Age range	Ratio (95% CI)	P value	Risk difference/1000 (95% CI)	P value
Ideation or worse				
<25 *v* ≥25	2.05 (1.26 to 3.34)	0.004	6.19 (1.76 to 10.6)	0.006
25-64 *v* ≥65	2.14 (1.08 to 4.24)	0.03	3.81 (0.34 to 7.28)	0.03
Ideation alone				
<25 *v* ≥25	1.84 (0.92 to 3.67)	0.08	2.75 (−0.61 to 6.12)	0.11
25-64 *v* ≥65	1.45 (0.65 to 3.27)	0.37	1.55 (−1.30 to 4.40)	0.29
Preparation or worse				
<25 *v* ≥25	2.57 (1.07 to 6.15)	0.04	3.43 (0.51 to 6.36)	0.02
25-64 *v* ≥65	13.8 (1.61 to 118)	0.02	2.42 (0.47 to 4.37)	0.02

Results of other studies

Several case-control studies have addressed the question of a differential risk of antidepressant induced suicidality across the age spectrum. Olfson et al found that antidepressant treatment was not associated with suicide attempts or suicide in severely depressed adults requiring admission to hospital.[10] In patients aged 6-18, however, there was a significant association with drug treatment and both suicide attempts and completed suicide. Martinez et al found no overall difference in risk between SSRIs and tricyclics but did find a suggestion of an increased risk of suicidality in patients aged 18 and younger.[11] Juurlink et al found greater risk of suicide in patients treated with an SSRI compared with patients receiving other antidepressants only in the first month of treatment.[12] The case-control methods used in these studies is subject to confounding—notably, differential prescribing to patients perceived to be sicker and at greater risk of suicidal behaviour.

Apart from the finding of age related risk, the results are consistent with published meta-analyses of clinical trials of SSRIs in adults conducted by Gunnell et al[5] and Fergusson et al.[6] Despite considerable differences in the availability of data, statistical methods, and event classification, the odds ratios were remarkably similar to those we obtained in subsets of our data that were most comparable with those used by these authors: odds ratios for SSRIs compared with placebo were 0.85[5] versus 0.86 (current study) for completed suicide, 1.29[5] versus 1.25 for non-fatal self harm, and 0.79[5] versus 0.76 for suicidal ideation. For a comparison of SSRIs with tricyclics the odds ratios for fatal or non-fatal suicide attempts were 0.88[6] versus 1.11 (current study).

Numerous population based studies in recent years have compared patterns of antidepressant prescribing and suicide rates.[13] Studies in Finland, Sweden, Hungary, Australia, one study in Britain, and a Europe-wide study showed an inverse correlation between antidepressant use and suicide rates, but studies in Italy, Iceland, and Denmark did not show a relation. A study from Northern Ireland showed an inverse correlation in adults over age 30 but found no relation between antidepressant use and suicide in adults aged 20-30.[14] In England and Wales Gunnell et al found no decrease in suicides among men aged 25-34, despite a small increase in antidepressant prescribing, but a large reduction in suicide rates in adults over 60 that correlated with increased antidepressant use.[15] In the US, Gibbons et al looked at county-level suicide rates with adjustments for age, sex, income, and race.[16] There was no overall relation with antidepressant prescribing, but the prescribing of SSRIs and other newer antidepressants was associated with lower suicide rates and tricyclic prescribing was associated with increased suicide rates. Grunebaum et al noted a fourfold increase in antidepressant prescribing coincident with an overall decrease in the suicide rate of 13.5% from 1985 to 1999.[17] Milane et al looked at fluoxetine prescribing between 1988 and 2002 and observed a decline in suicide rates since its introduction.[18] The findings in non-US studies were generally similar. The ecological approach taken by these studies, however, does not allow causal conclusions. For example, increased use of SSRIs and lower suicide rates could both be consequences of economic prosperity or greater availability of mental health services.

Explanations and implications

Some have argued that an observed increase in suicidality with drug treatment could be the result of ascertainment bias: an increase in reporting of suicidality rather than a true increase. This could occur if people were so depressed that they could not articulate suicidal thoughts or report suicidal behaviour until relief was obtained from drug treatment or if they reported suicidal thinking or behaviour only because they also sought medical attention for drug side effects. This effect would need to be greater than a similar bias that could operate in the opposite direction: people in a placebo group who, because of lack of therapeutic effect, sought treatment for non-suicidal symptoms and, when examined, disclosed suicidal symptoms as well. Our findings argue against this explanation. Ascertainment bias cannot easily explain the observed age relatedness of the findings or the stronger apparent increase in suicidality in non-depressed psychiatric patients in the youngest age group than in depressed patients of the same age. It also cannot explain an apparently greater effect on promoting the reporting of suicidal behaviour than the reporting of suicidal ideation.

The association of antidepressant treatment with an increased risk of suicidality and suicidal behaviour seems paradoxical. If suicide is a response to the symptoms of depression, treatments proved to reduce these symptoms ought to reduce the risk of suicide. Our study suggests, however, that the relation between suicidality, age, and antidepressant treatment is generalisable beyond those with major depressive disorder to

Table 8 | Change per year of age for drug effect on suicidality

Outcome	Change in odds ratio (95% CI)	P value
Ideation or worse	−2.6% (−3.9% to −1.3%)	0.0001
Ideation alone	−1.8% (−3.3% to −0.4%)	0.01
Preparation or worse	−4.6% (−7.4% to −1.8%)	0.001

Table 9 | Suicidality risk for active drug relative to placebo by age and diagnostic category

	Age <25		Age 25-64		Age ≥65	
Diagnostic category	Estimate (95% CI)	P value	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Odds ratio						
Ideation or worse:						
Major depressive disorder	1.46 (0.70 to 3.07)	0.31	0.89 (0.68 to 1.16)	0.38	0.38 (0.19 to 0.79)	0.01
Other depression	1.10 (0.18 to 6.56)	0.92	0.84 (0.31 to 2.30)	0.74	No events	—
Other psychiatric disorders	1.92 (0.88 to 4.20)	0.10	0.61 (0.41 to 0.89)	0.01	One event	—
Ideation alone:						
Major depressive disorder	1.56 (0.56 to 4.35)	0.40	0.74 (0.54 to 1.01)	0.06	0.56 (0.26 to 1.24)	0.15
Other depression	One event	—	1.06 (0.34 to 3.30)	0.92	No events	—
Other psychiatric disorders	1.07 (0.40 to 2.81)	0.90	0.64 (0.41 to 0.99)	0.04	One event	—
Preparation or worse:						
Major depressive disorder	1.36 (0.47 to 3.96)	0.40	1.41 (0.83 to 2.38)	0.20	0.06 (0.01 to 0.58)	0.01
Other depression	2.07 (0.22 to 19.5)	0.52	0.32 (0.03 to 3.56)	0.35	No events	—
Other psychiatric disorders	4.82 (1.08 to 21.4)	0.04	0.51 (0.22 to 1.18)	0.11	No events	—
Risk difference/1000 participants						
Ideation or worse:						
Major depressive disorder	4.53 (−2.76 to 11.8)	0.22	−1.00 (−2.95 to 0.95)	0.32	−7.32 (−12.6 to −2.04)	0.01
Other depression	5.00 (−37.2 to 47.2)	0.82	−0.51 (−4.32 to 3.30)	0.79	No events	—
Other psychiatric disorders	5.73 (−0.30 to 11.8)	0.06	−2.51 (−4.59 to −0.42)	0.02	−3.84 (−8.81 to 1.13)	0.13
Ideation alone:						
Major depressive disorder	3.49 (−1.95 to 8.94)	0.21	−1.61 (−3.28 to 0.06)	0.06	−3.71 (−7.91 to 0.50)	0.08
Other depression	−11.5 (−29.4 to 6.42)	0.21	0.25 (−3.09 to 3.58)	0.88	No events	—
Other psychiatric disorders	0.79 (−4.00 to 5.58)	0.75	−1.82 (−3.67 to 0.03)	0.05	−3.84 (−8.81 to 1.13)	0.13
Preparation or worse:						
Major depressive disorder	0.91 (−4.09 to 5.92)	0.72	0.60 (−0.41 to 1.60)	0.24	−3.41 (−6.25 to −0.57)	0.02
Other depression	19.1 (−17.0 to 55.2)	0.30	−0.76 (−2.51 to 1.00)	0.40	No events	—
Other psychiatric disorders	5.11 (1.31 to 8.91)	0.01	−0.59 (−1.50 to 0.32)	0.20	No events	—

everyone with psychiatric diagnoses. These findings support the idea that antidepressant drugs can have two separate effects: an undesirable effect in some patients that promotes suicidal ideation or suicidal behaviour and a therapeutic effect in others that alleviates depression and reduces any suicidal sequelae from depression. From the standpoint of clinical decision making, the age dependent increase in suicidality would be considered a phenomenon separate from therapeutic effect and approached like any other uncommon but serious adverse effect. Patients whose illnesses pose less risk of suicidal ideation or behaviour, such as those without major depression, could have less potential to benefit from any effect drug treatment might have on reducing suicidal sequelae but be little different from patients with major depression in vulnerability to adverse effects.

The possibility of separate therapeutic and adverse effects from antidepressant drugs on suicide ideation or behaviour should be the subject of further research, particularly in terms of possible mechanisms for age related differences. Another possible topic for investigation would be differences among drugs. Although this study did not show much evidence for differences between antidepressant drugs in net effect on suicidal behaviour or ideation, further investigation could reveal whether some drugs cause relatively substantial increases in both adverse and therapeutic effects while other drugs have little effect on either.

When we presented these results at a meeting of the Psychopharmacologic Drugs Advisory Committee in December 2006 [www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf], the committee agreed with FDA's conclusions that the risk of suicidality associated with antidepressants in young adults (under 25) approached that seen in children and adolescents, that the net effect seemed to be neutral in adults aged 25-65, and that the effect on suicidality was favourable in adults older than 65. They

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trials of antidepressants in children and adolescents have shown an increased risk of suicidal thoughts or behaviour relative to those who received placebo.

Epidemiological studies have tended to show an association of lower rates of suicide with higher rates of antidepressant use

WHAT THIS STUDY ADDS

Effects on suicidal thoughts or behaviour associated with antidepressants observed in clinical trials are strongly age dependent; risk declines and benefit increases with increasing age

The age related gradient seems steeper for suicidal behaviour than for ideation alone

Beneficial effects on suicidal thoughts and ideation were most strongly associated with older people treated for major depression, whereas harmful effects were most strongly associated with younger people treated for psychiatric disorders other than depression

recommended that the FDA should expand the suicidality warning language in labelling and in the medication guide with this new information, including the strong age relatedness of the findings. Because of concerns of a possible negative impact of the FDA's regulatory actions on appropriate treatment of depression, especially in younger patients, the committee also recommended that the warnings on the labelling and in medication guides include language making clear that depression is a serious illness that itself is a strong predictor of suicide. These changes to labelling and medication guides have now been implemented.

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1 Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. *Arch Gen Psychiatry* 2000;57:311-7.
2 Storosum JG, van Zweiten BJ, van den Brink W, Gersons BPR, Broekmans AW. Suicide risk in placebo-controlled studies of major depression. *Am J Psychiatry* 2001;158:1271-5.
3 Hammad T, Laughren T, Racoosin JA. Suicide rates in short-term randomized controlled trials of newer antidepressants. *J Clin Psychiatry* 2006;26:203-7.
4 Hammad T, Laughren T, Racoosin JA. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006;63:332-9.
5 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitiors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomized controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385-90.
6 Fergusson D, Douchette S, Cranley Glass K, 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.
7 Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035-43.
8 Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. *Methods for meta-analysis in medical research*. Chichester: John Wiley, 2000.
9 Rucker G, Schwarzer G, Carpenter C, Olkin I. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. *Stat Med* 2009;28:721-38.
10 Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults. *Arch Gen Psychiatry* 2006;63:865-72.
11 Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* 2005;330:389-93.
12 Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatry* 2006;163:813-21.
13 Hall WD, Lucke J. How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? *Aust N Z J Psychiatry* 2006;40:941-50.
14 Kelly CB, Ansari T, Rafferty T, Stevenson M. Antidepressant prescribing and suicide rate in Northern Ireland. *Eur Psychiatry* 2003;18:325-8.
15 Gunnell D, Middleton N, Whitley E, Dorling D, Frankel S. Why are suicide rates rising in young men but falling in the elderly?—a time-series analysis of trends in England and Wales 1950 to 1998. *Soc Sci Med* 2003;57:595-611.
16 Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry* 2005;62:165-172.
17 Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ. Antidepressants and suicide risk in the United States, 1985-1999. *J Clin Psychiatry* 2004;65:1456-62.
18 Milane MS, Suchard MA, Wong M, Licinio J. Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. *PLoS Med* 2006;3:1-9.

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