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Suicides and Suicide Attempts during Long-Term Treatment with Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients with Major Depressive Disorder

Cora Braun[a] Tom Bschor[c, d] Jeremy Franklin[b] Christopher Baethge[a]

[a]Department of Psychiatry and Psychotherapy and [b]Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne Medical School, Cologne, [c]Department of Psychiatry, Schlosspark Hospital, Berlin, and [d]Department of Psychiatry and Psychotherapy, Technical University of Dresden Medical School, Dresden, Germany

Key Words
Suicide · Suicide attempt · Suicidality · Antidepressants · RCT · Maintenance

Abstract
Background: It is unclear whether antidepressants can prevent suicides or suicide attempts, particularly during long-term use. ***Methods:*** We carried out a comprehensive review of long-term studies of antidepressants (relapse prevention). Sources were obtained from 5 review articles and by searches of MEDLINE, PubMed Central and a hand search of bibliographies. We meta-analyzed placebo-controlled antidepressant RCTs of at least 3 months' duration and calculated suicide and suicide attempt incidence rates, incidence rate ratios and Peto odds ratios (ORs). ***Results:*** Out of 807 studies screened 29 were included, covering 6,934 patients (5,529 patient-years). In total, 1.45 suicides and 2.76 suicide attempts per 1,000 patient-years were reported. Seven out of 8 suicides and 13 out of 14 suicide attempts occurred in antidepressant arms, resulting in incidence rate ratios of 5.03 (0.78–114.1; p = 0.102) for suicides and of 9.02 (1.58–193.6; p = 0.007) for suicide attempts. Peto ORs were 2.6 (0.6–11.2; nonsignificant) and 3.4 (1.1–11.0; p = 0.04), respectively. Dropouts due to unknown reasons were similar in the antidepressant and placebo arms (9.6 vs. 9.9%). The majority of suicides and suicide attempts originated from 1 study, accounting for a fifth of all patient-years in this meta-analysis. Leaving out this study resulted in a nonsignificant incidence rate ratio for suicide attempts of 3.83 (0.53–91.01). ***Conclusions:*** Therapists should be aware of the lack of proof from RCTs that antidepressants prevent suicides and suicide attempts. We cannot conclude with certainty whether antidepressants increase the risk for suicide or suicide attempts. Researchers must report all suicides and suicide attempts in RCTs.
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Introduction

In the long run, a considerable number of patients with depressive disorders die of suicide. In the Zurich cohort of initially hospitalized patients, roughly 15% of individuals with major depressive disorder had committed suicide after 50 years [1]. Over the same period of time, the risk

The results of this study were presented at the 29th IGSLi Conference in Aalborg, Denmark, in September, 2015.

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Christopher Baethge, MD, Professor of Psychiatry
Abteilung für Psychiatrie und Psychotherapie
Universitätsklinikum Köln
Kerpener Str. 62, DE–50937 Köln (Germany)
E-Mail cbaethge@uni-koeln.de

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of completed suicide in a Swedish community sample of patients with depression averaged approximately 6%, whereas the risk amounted to 14% in the subgroup of patients with severe major depressive disorder [2]. In a model based on 27 studies on mortality in affective disorders, Inskip et al. [3] estimated the lifetime risk of suicide to be 6%. Suicidal acts mostly occur during acute illness episodes and in the beginning of the disorder [4].

Although the debate continues about their effect size, antidepressants have repeatedly been shown to be effective psychotropic agents in depression [for overviews, see 5, 6]. It is hoped, therefore, that antidepressants also reduce the risk of suicide. In this sense, the European Psychiatric Association, in their 'guidance on suicide treatment and prevention', state that antidepressants decrease suicidality [7].

Unfortunately, data regarding the effect of antidepressants on suicidality are inconclusive. In depressed patients undergoing antidepressant maintenance therapy, Angst et al. [8] reported a statistically significantly lower suicide rate relative to untreated patients. In the same vein, other authors concluded from epidemiological and observational data that antidepressant use lowers the risk of suicide [7, 9, 10]. However, even a positive association of antidepressant prescription and suicide rate has been reported [11]. Epidemiological and observational studies, however, are vulnerable to confounding bias. This disadvantage seems especially relevant for suicide and suicide attempts. The complexity of this behavior is illustrated by the difficulties in predicting suicides and suicide attempts with sufficient certainty – despite a host of risk factors that have been published [12–15]. For an overview of methodological difficulties in suicide research, see the study by de Leon et al. [16].

Suicidal behavior is often not a stated outcome measure in antidepressant studies, and these studies are not designed for comparing suicide rates. Nevertheless, randomized trials of antidepressant pharmacotherapy lend themselves to analyses with regard to suicidality. For example, Gibbons et al. [17] report that fluoxetine and venlafaxine reduce suicidality, as measured primarily by using suicidality items on rating scales (HMA-D, CDRS-R). This is an indirect measurement considering that suicidal thoughts constitute the most part of what is considered suicidality in this analysis and that they are only weak predictors of completed suicides. However, completed suicides and suicide attempts matter most to patients. Interestingly, other authors did not find a beneficial effect of antidepressants on suicide in placebo-controlled acute treatment trials [18–24]. In addition, Storosum et al. [24] presented raw numbers of suicide and suicide attempts from several randomized long-term studies and concluded that their frequency was not higher in placebo groups.

Long-term studies of depressive disorders are of particular interest because many depressive disorders take a chronic course. It may also be hypothesized that an antisuicidal effect of antidepressants is more pronounced in long-term treatment because the placebo effect decreases and the effect size of antidepressants is relatively high. However, there is no comprehensive review of suicides and suicide attempts in randomized long-term antidepressant studies. As a consequence, we carried out a comprehensive review and meta-analysis of placebo-controlled long-term studies. The analysis accounts for different exposure times, sample sizes and dropout rates in antidepressant and placebo arms.

Methods

This is a literature review and meta-analysis on suicide and suicide attempts in placebo-controlled randomized trials of long-term treatment of major depressive disorder with antidepressants.

Literature Search

The initial search was based on 5 reviews on antidepressant long-term treatment, three systematic reviews and meta-analyses [25–27] and two narrative reviews [24, 28]. In order to cover the time that passed after the search for the reviews had been finished, we updated 2 of the searches in MEDLINE and PubMed Central via PubMed. The search by Glue et al. [26] was updated on September 28, 2014 (from August 25, 2008 onwards) using the following search history: *(discontinuation [Title/Abstract] OR continuation [Title/Abstract]) AND (prevention [Title/Abstract]) AND (relapse [Title/Abstract]) AND (major depressive disorder [Title/Abstract]).*

The search by Geddes et al. [25] was updated on March 24, 2015 (from July 31, 2000 onwards) using the following search history: *(drug Therapy [MeSH Major Topic] OR antidepr* [Title/Abstract]) AND (depression* [Title/Abstract] OR depressive-disorder [Title/Abstract] OR dysthymi* [Title/Abstract]) AND (maintenance* [Title/Abstract] OR maintain* [Title/Abstract] OR long-term [Title/Abstract] OR continu* [Title/Abstract] OR preventive [Title/Abstract]) AND (randomized controlled trial [Publication type]).*

There were no language restrictions. We did not exclude gray literature. Titles and abstracts of studies retrieved were screened, and all possibly relevant texts were read to judge their eligibility. Reference lists of eligible trials were hand-searched.

Study Selection

We selected studies on patients with depressive disorders (diagnosed with a commonly applied diagnostic system) randomized to receive antidepressants or placebo for at least 3 months. Although in these studies the main outcomes were psychopathological variables, we restricted our selection process to studies reporting on suicides (primary outcome) and suicide attempts (secondary outcome) during treatment.

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Data Collection

Bibliographical information, key study characteristics, such as sample size, age or dropouts, and outcomes (number of suicides and suicide attempts per arm, number of follow-ups per arm) were extracted into an Excel spreadsheet. All corresponding authors of trials that were eligible but lacked data on suicides or suicide attempts were repeatedly approached by e-mail or regular mail.

Analysis

In most studies neither suicides nor suicide attempts were reported. Classical meta-analytic calculations, such as those based on estimates of odds ratios (ORs), assume at least 1 event. Not including studies without events, however, would have resulted in an overestimation of the risk of suicides and suicide events. Therefore, the main analysis was based on incidence rates. Incidences of suicides and suicide attempts were documented as raw numbers per study and calculated as events per 1,000 patient-years (incidence rate). From incidence rates rate ratios and p values (mid-p exact) were calculated. For completeness, we also calculated summary estimates based on studies reporting at least 1 event: Peto ORs, as a measure of rare events [29], were calculated. Between-study heterogeneity is presented as the I^2 statistic. All analyses were conducted using Excel, OpenEpi (www.openepi.com) and Comprehensive Meta-Analysis, version 2 (CMA 2). Suicide and – to a lesser extent – suicide attempts are hard outcomes. Thus, we did not assess the risk of bias.

Additional post hoc Analysis

In the first of two subgroup analyses we left out 1 study that contributed a large number of cases. In the second analyses we recalculated event rates without 6 studies on pediatric samples and older patients. In a sensitivity analysis we adjusted the overall suicide rate for dropouts.

Results

Through reviews of antidepressant maintenance treatment RCTs [24–28] and through our own MEDLINE and PubMed Central search 807 papers were identified for screening after duplicates were removed. Eighty-five reports were read as full text. In total, the authors had reported in 65 papers on various studies of antidepressant maintenance trials, but 36 of these had not documented suicides or suicide attempts or had not provided data upon request. The following 29 studies were included in our quantitative analysis: Blumenthal et al. [30], Cheung et al. [31], Doogan and Caillard [32], Emslie et al. [33], Feiger et al. [34], Goodwin et al. [35], Kamijima et al. [36], Kishimoto et al. [37], Klysner et al. [38], Kornstein et al. [39], Lepine et al. [40], Licht et al. [41], Lustman et al. [42], McGrath et al. [43], Montgomery et al. [44], Montgomery and Dunbar [45], Old Age Depression Interest Group [46], Perahia et al. [47], Reynolds et al. [48], Robinson et al. [49], Rosenthal et al. [50], Rouillon et al. [51], Schmidt et al. [52], Shiovitz et al. [53], Stewart et al. [54], Terra and Montgomery [55], Thase et al. [56], Versiani et al. [57], Weihs et al. [58].

Online supplementary figure 1 presents the PRISMA flowchart (for all online supplementary material, see www.karger.com/doi/10.1159/000442293).

All included studies were published between 1989 and 2014. The studies included 6,934 patients (4,016 in antidepressant arms and 2,918 patients in placebo arms, respectively) and covered 5,529.06 patient-years (3,218.24 and 2,310.82, respectively). Two thirds of patients were women (67.2%), and the mean age was 46.6 (SD: 10.6) years.

Antidepressants studies included the following: nefazodone (1×), sertraline (6×), fluoxetine (3×), mianserin (1×), citalopram (3×), clomipramine (1×), escitalopram (1×), duloxetine (2×), maprotiline (1×), paroxetine (1×), fluvoxamine (1×), mirtazapine (1×), reboxetine (1×), desvenlafaxine (1×), bupropion (1×), dothiepin (1×), nortriptyline (1×), phenelzine or imipramine (1×), agomelatine (1×) and levomilnacipran (1×). One study [41] had one citalopram and one clomipramine arm. All papers described maintenance treatment trials of patients with major depressive disorder, with the exception of Stewart et al. [54] and Rouillon et al. [51], who also included patients with dysthymia. In almost all studies randomization took place *after* response or remission was ascertained by the study authors. The exception is the trial by Blumenthal et al. [30], but in this trial no acute treatment phase preceded long-term treatment. Online supplementary table 1 summarizes the characteristics of all studies selected.

In total, 8 suicides and 14 suicide attempts were reported in all studies combined, resulting in 1.45 suicides (95% CI: 0.62–2.85) and 2.76 suicide attempts (95% CI: 1.51–4.63) per 1,000 patient-years. Seven out of 8 suicides and 13 out of 14 suicide attempts occurred in antidepressant arms. Adjusted for years exposed, suicides were 5 times ($p = 0.102$) and suicide attempts 9 times ($p = 0.007$) more likely in antidepressant arms than in placebo arms (see table 1 for incidence rates and rate ratios). Six of 8 suicides and 9 of 14 suicide attempts were reported in one study, that of Rouillon et al. [51]. Events were reported in 6 studies. All had excluded patients with bipolar disorder, except for the study by Doogan and Caillard [32], with roughly 5% of bipolar patients in the sample.

In meta-analyses of studies with at least 1 event we estimated Peto OR to be 2.6 (0.6–11.2; $p = 0.21$) for suicides and 3.4 (1.1–11.0; $p = 0.040$) for suicide attempts. Heterogeneity among studies included in the meta-analysis was low (I^2 values of 0 and 4%, respectively; see forest plots in fig. 1, 2).

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Table 1. Incidences and rate ratios of suicide and suicide attempts in long-term randomized trials comparing antidepressants and placebo

	Antidepressant	Rate ratio	Placebo
Suicides			
Incidence per 1,000 patient-years (n = 29 studies)	2.18 [0.87–4.48]		0.43 [0.006–2.41]
Rate ratio (n = 29 studies)	5.03 [0.78–114.1]	p = 0.102	
Suicide attempts			
Incidence per 1,000 patient-years (n = 25 studies)	4.34 [2.31–7.42]		0.48 [0.006–2.67]
Rate ratio (n = 25 studies)	9.02 [1.58–193.6]	p = 0.007	

Values in square brackets are 95% CI. Rate ratios are calculated from incidence rates (conditional maximum likelihood estimate), two-sided p values (mid-p exact).

Slightly more patients had dropped out from placebo arms than from antidepressant arms: 31.1 versus 26.7%. Dropouts for unknown reasons were equally distributed between arms: 9.9% (placebo) versus 9.6% (antidepressants), respectively.

Post hoc Analyses

In a sensitivity analysis adjusting for dropouts we approximated an overall rate of 1.69 suicides/1,000 patient-years (antidepressants: 2.51, placebo: 0.51).

After omitting the study by Rouillon et al. [51] the estimate for suicides in antidepressant arms fell to 0.82 suicides per 1,000 patient-years (0.09–2.95) and to zero suicides in placebo arms (0–1.89). Accordingly, the risk difference was 0.82 (–0.31 to 1.95). The figures for suicide attempts were 2.24 per 1,000 patient-years under antidepressants (0.72–5.23) versus 0.59 (0.008–3.26), with suicide attempts in antidepressant arms more likely by a factor of almost 4 at 3.83 (0.53–91.01; statistically nonsignificant).

In another subgroup analysis we left out 6 studies of pediatric and geriatric samples. There were 2.45 (0.98–5.04) suicides per 1,000 patient-years in antidepressant arms and 0.50 (0.007–2.78) in placebo arms, with a rate ratio of 4.91 (0.76–111.4). Figures for suicide attempts in antidepressant versus placebo arms were 4.36 (2.25–7.61) versus 0.56 (0.007–3.13), with a rate ratio of 7.73 (1.34–166.8).

Discussion

This study yielded several important results. Firstly, only a minority of papers on randomized, long-term antidepressant therapy studies contained data on suicides and suicide attempts. Secondly, during approximately 5,500 patient-years suicides and suicide attempts did occasionally occur: roughly 1.5 suicides among 1,000 patients per year and twice as many suicide attempts. Thirdly, the incidence rates of suicide and suicide attempts were higher among patients treated with antidepressants than among patients randomized to placebo: suicides occurred 5 times more often (statistically nonsignificant) and the risk of suicide attempts was 9-fold (statistically significant) in antidepressant arms.

Underreporting of Events

Many papers on long-term treatment with antidepressant did not contain information on suicides and suicide attempts among participants. Unfortunately, it cannot be assumed that no events occurred only because authors do not report on suicide and suicide attempts. For example, whereas we could not find pertinent data in the paper by Licht [41], upon request, the author kindly provided us with the information that in their study 3 patients had attempted suicide. Accordingly, the present study is restricted to studies with information on suicides and suicide attempts. Similar to our experience, Fergusson et al. [23], in their meta-analysis of suicide attempts under SSRIs, found that less than half of all trials reported on suicide attempts. They also concluded that 'a substantial proportion of suicide attempts have gone unreported'. It is conceivable that the situation is not much different in our set of RCTs. However, in an investigation of discrepancies between clinical study reports (as submitted to the European Medicines Agency, EMA) and published journal articles, Maund et al. [59] found no underreporting of suicides and suicide attempts in papers with respect to duloxetine trials. In a similar project, Hughes et al. [60],

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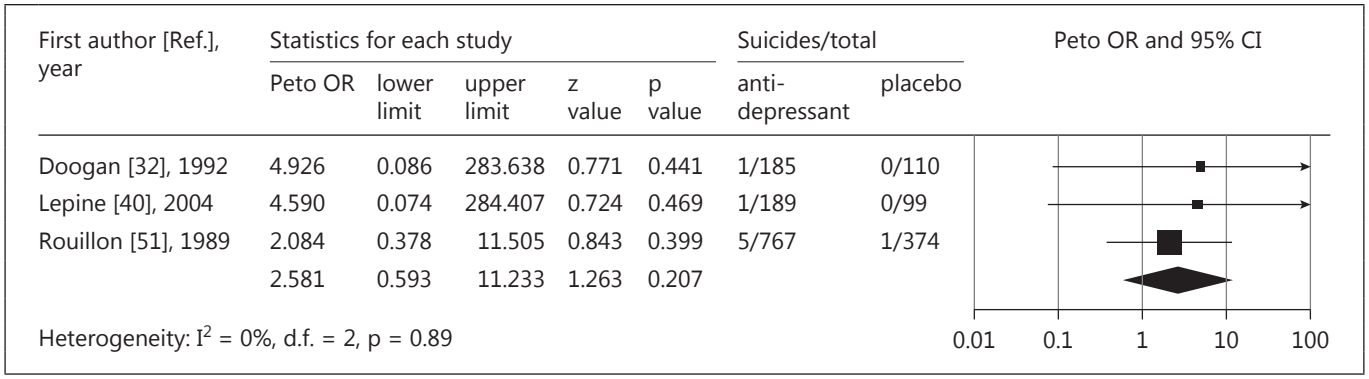

Fig. 1. Forest plot of studies documenting suicide events.

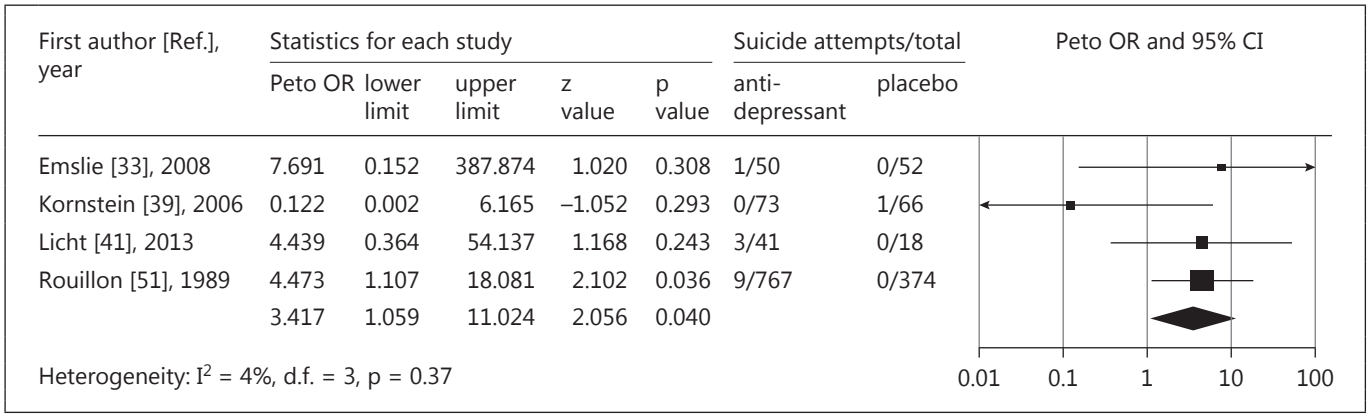

Fig. 2. Forest plot of studies documenting suicide attempt events.

on the other hand, documented underreporting of suicide attempts (but not completed suicides) regarding duloxetine and sertraline trials.

Incidence Rates

Among the studies included almost a tenth of patients dropped out for reasons unknown to the investigators. It is possible that events did occur in this subgroup and, in principle, that they would have changed the results. The rate of dropouts due to unknown reasons, however, was the same among patients on antidepressants and on placebo – rendering different dropout patterns unlikely.

Even if suicides and suicide attempts did occur, statistically, the number of events reported in the studies selected for this review is small, making precise inferences difficult. They are, however, in the order of magnitude of epidemiological estimates of suicide prevalence in major depressive disorder. A 6% suicide rate over 50 years [2, 3] translates into 1.2 suicides/1,000 patient-years. In comparison, the summary suicide rate in our meta-analysis was 1.45/1,000 patient-years (0.43 under placebo and 2.18 under antidepressants).

In contrast, our estimate of the suicide *attempt* rate is lower than that expected from the literature: Isometsä [4], emphasizing considerable variation among studies, concluded that the lifetime prevalence of suicide attempts in major depressive disorder amounts to 30–40%, equal to 6–8 attempts per 1,000 patients per year. From our studies, however, we calculated 2.76 suicide attempts per 1,000 patient-years. Suicide attempts may be underreported in the studies included. The rate of 1.45 suicides/1,000 patient-years is probably an underestimation because, similar to other studies in this field, dropouts – roughly 30% of the samples – were not factored in.

These findings are surprising in view of the concern that RCTs may not be appropriate in estimating suicide

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risks because they tend to exclude patients at risk for suicide [9]. Among the 29 studies in this overview, however, only 12 mentioned such an exclusion criterion, although all investigators may have tried to exclude suicidal patients to limit liability. What seems even more important is that, unfortunately, suicides and suicide attempts are exceedingly difficult to predict [12–15]. Hence, even the exclusion of patients considered to be at risk is unlikely to result in substantial risk reductions for samples as a whole.

In most meta-analyses of acute treatment RCTs, the numbers of events are larger than in our calculation. Khan et al. [22], for example, calculated 6.6 suicides per 1,000 exposure years, with no statistically significant differences in the number of suicides under antidepressants and under placebo. The most likely explanation is that acute psychopathology as a risk factor for suicide is more severe in acute treatment studies.

In sum, although RCTs are different from everyday clinical care in several ways, the summary suicide risk estimate seems similar to what is known from epidemiological studies. In our opinion, the unquestioned advantage of RCTs over observational studies in preventing bias makes them the most important source for estimating suicide risk reduction under antidepressants.

The Maprotiline Study by Rouillon et al. [51]

The majority of suicides and suicide attempts in our analyses originated from one study [51]. This study is important because it is by far the largest one, accounting for about a fifth of the data (20.6% of patient-years). There is no reason to treat this study differently from the others just because several events happened in the course of this drug trial. However, the study stands out in several ways: it is the earliest study selected, it is one of 2 studies including patients with dysthymia, and it is the only study that compared the tetracyclic compound maprotiline with placebo. Maprotiline has been associated with suicide in observational studies [61]. White et al. [62], analyzing US poison control data from more than 80,000 suicidal overdoses, reported maprotiline as among rarely used substances (19 events) but with a particularly high fatality rate ('hazard index'). This study runs counter to an earlier paper by Henry and Antao [63] from the UK that reported maprotiline to be safer than average in overdose. Already in the 1990s, however, in a Swiss study maprotiline figured prominently among antidepressants used for suicide [64]. In our post hoc sensitivity analysis leaving out the Rouillon study, rate ratios decreased, but the results weakly and statistically nonsignificantly favored placebo.

No Evidence for Protective Effects of Antidepressants

Our result of a lack of proof regarding a protective effect of antidepressants on suicide or suicide attempts is in line with meta-analyses primarily focusing on acute treatment studies: none of the 8 meta-analyses of antidepressant RCTs known to the authors resulted in statistically significant superiority compared to placebo [18–23, 65, 66]. The suicide event rate is low, precluding definite conclusions, but if there is any signal from these meta-analyses, it is that there may be a marginal suicide risk *increase* with antidepressants. For example, Stone et al. [65], in their comprehensive FDA analysis, found a slightly higher suicide rate among patients with major disorders in antidepressant arms (5/30,707 vs. 1/14,873 in placebo arms, nonsignificant). However, while the comparisons in those studies tended to numerically favor placebo over various antidepressants, with the exception of Hammad et al. [19], only few studies found antidepressants to be statistically significantly inferior to placebo. Fergusson et al. [23], in a study on suicide attempts, reported such an inferiority for SSRIs. Similarly, Carpenter et al. [66], analyzing the GlaxoSmithKline paroxetine clinical trials database, found more 'definitive suicidal behavior' (suicides, suicide attempts and preparatory acts toward imminent suicidal behavior) under active medication than under placebo among patients with major depressive disorder: OR 6.7 (1.1–149.4), but not in other indications. It has to be borne in mind that most of the trials on which these meta-analyses rest are short-term studies. However, the focus of our analysis is on long-term studies, which differ in many respects, for example in the fact that patients are remitted at study entry. In addition, phenomena such as loss of antidepressant efficacy [67], the development of tolerance [67] and withdrawal symptoms [68] may be important in interpreting long-term studies.

Based on long-term trials presented to the regulatory drug authority in the Netherlands as well as retrieved through a literature review, Storosum et al. [24] concluded that placebos are not associated with higher risks for suicide or suicide attempts than antidepressants. The authors, in their evaluation of the study by Versiani et al. [57], erroneously assigned 1 suicide to the active compound (reboxetine) that, in fact, occurred before randomization. However, this error is inconsequential with regard to their conclusions.

It is unlikely that a general lack of antidepressant efficacy is the reason for a possible lack of *antisuicidal* efficacy of antidepressants. On the contrary, 3 systematic and 1 narrative reviews that form part of the basis of this meta-analysis reported that antidepressants are superior to placebo in preventing relapses [25–28].

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Limitations

Several limitations of our study have to be borne in mind. In many studies, enriched and withdrawal designs were chosen, which may have been an advantage for antidepressants. Since this study used published articles we could not adjust for dropout rates on an individual level. While it is difficult to predict how such adjustments would affect the differences between antidepressants and placebo, it is plausible that the true event rates would be higher than those observed, and that we present conservative estimates of suicide and suicide attempt incidence rates. In addition, further subgroup analyses, meta-regressions or other predictor searches would have been desirable, but the low number of events and the nonavailability of subgroup or individual patient data precluded further calculations.

We could have missed important studies, but to our knowledge this is the largest meta-analysis of randomized antidepressant long-term studies so far. Meta-analyses, however, often put together a heterogeneous set of studies but arrive at a global effect estimate [69]. In this sense, we have treated antidepressants as a homogeneous group, but it is certainly possible that different compounds behave differently. At least, we found preliminary evidence that maprotiline may constitute a particular risk. However, in principle, it would be desirable to analyze data for every antidepressant specifically (as has been done, for example, for paroxetine [66] or for venlafaxine and citalopram [21]). For the time being, however, there is no viable alternative to meta-analyzing all the data that are available.

Conclusions

In conclusion, we found no evidence from randomized trials of long-term antidepressant treatment that, as a group, antidepressants prevent suicide or suicide attempts among patients with major depressive disorder. The rate of patients killing themselves during the studies under investigation is in the order of magnitude expected from epidemiological models. Doctors and patients should be aware of this finding and should not rely solely on antidepressants in dealing with suicidality. Close clinical monitoring of patients at risk for suicide is imperative. A psychopharmacological option in the prevention of suicide is lithium [70].

We cannot exclude that antidepressants carry a *higher* risk of suicide or suicide attempts than placebo. It is of paramount importance for future research that all papers reporting on randomized antidepressant studies contain information on suicides and suicide attempts.

Disclosure Statement

This study has not been funded by any external institution or company. Cora Braun, Jeremy Franklin and Christopher Baethge declare that they have no conflicts of interest according to the definition of the International Committee of Medical Journal Editors (ICMJE). Tom Bschor has received honoraria for talks or lectures from Lilly, AstraZeneca, Esparma, Bristol-Myers Squibb, Sanofi-Aventis, Servier and Lundbeck, and has accepted reimbursements of travelling expenses to congresses from AstraZeneca and Lilly.

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