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REVIEW

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Is there evidence for negative effects of antidepressants on suicidality in depressive patients?

A systematic review

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Abstract The role of antidepressants in suicide prevention is a major public health question given the high prevalence of both depression and depression-related suicidality. Therefore all available means should be utilised to clarify the influence of antidepressants on suicidality, especially in view of the ongoing intensive debate about possible suicidality-inducing effects of antidepressants that may outweigh their traditionally hypothesised beneficial effects. This paper gives a systematic and comprehensive review of the empirical data which might indicate that antidepressants have negative effects on suicidality. First, principal methodological issues related to this research question are discussed. Thereafter, the results of controlled trials and epidemiological and cohort studies are presented. Altogether, there seems to be only a small amount of evidence from different research approaches that antidepressants, not only serotonin reuptake inhibitors (SSRIs), might induce, aggravate or increase the risk of suicidal ideation and suicide attempts. As to suicide, there are no hints in this direction. TCAs have a higher risk of fatal outcome in overdose compared to SSRIs, which, in case of mono-intoxication, carry almost no risk of lethal consequences. The ongoing discussion about suicidality-inducing effects should not prevent physicians from prescribing SSRIs and other antidepressants to their patients if they are clinically indicated. However, they should take into account potential risks and manage them by good clinical practice.

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Introduction

On the basis of clinical experience psychiatrists tend to have the view that antidepressants not only alleviate depressive symptoms but also reduce suicidality [1]. This clinical view is supported by data from controlled clinical studies, which show that suicidal thoughts generally subside during treatment over the same space of time as depressive symptoms. However, only a limited number of controlled studies have investigated this question [2]. In addition, data from epidemiological studies also provide some evidence for a suicide-preventive action of antidepressants. Just recently an epidemiological study came to the conclusion that the introduction of the selective serotonin reuptake inhibitors (SSRIs) in 1988 was temporally associated with a substantial reduction in the number of suicides in the USA [3]. Under certain conditions, antidepressants can possibly also induce or increase suicidal thoughts or behaviour. The respective data stem primarily from case reports. Recently, these case reports were backed up by the results of one meta-analysis on the available controlled studies, while others gave no indication in this direction.

In view of the fact that an intensive discussion is currently ongoing in paediatric psychiatry about the possibility that SSRIs might increase suicidal behaviour [4]—similar to the debate in adult psychiatry about 10 years ago [5]—it seems relevant to re-assess the data concerning a possible suicide-inducing effect of antidepressants. It is thereby important to strive for a balanced view in which possible risks are weighed against the therapeutic effects of antidepressants on suicidality. In this context, methodological problems

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in the empirical analysis of effects of antidepressants relevant for suicidality must be carefully considered in order to avoid reaching false conclusions concerning the risk/benefit ratio.

This paper gives a comprehensive overview of possible negative effects of antidepressants on suicidality. The first section will examine principal methodological issues related to investigating this issue in general. Thereafter, the results of clinical trials and epidemiological studies which test the hypothesis that antidepressants induce/increase suicidality will be presented and discussed. Based on this comprehensive review the paper will attempt to answer the question of the risk/benefit ratio.

The basis for this comprehensive review was an intensive MEDLINE search for publications related to the topics antidepressants, suicide, suicidality, suicidal behaviour and aggression. Manual searches of pertinent journal article references, and access of the website of the Food and Drug Administration and the European Medicines Agency, were also performed.

Methodological problems in analysing negative effects of antidepressants on suicidality

Given the fact that antidepressants represent an effective treatment for depressive patients, it was hypothesised that this treatment is not only effective in reducing depressive symptoms but also in reducing suicidality associated with depression [6, 7]. Although this view appears to be in accordance with general clinical experience, the data do not appear to be so robust from the perspective of evidence-based medicine [2]. On the other hand, there are data which suggest the opposite, i.e., that antidepressants have a suicidality inducing/increasing effect in depression and possibly also other conditions.

If one wants to investigate the question whether an antidepressant generally has a special influence on the risk of suicidal behaviour, one has to put the number of events in relation to the number of cases treated and to compare the resulting quotient with the risk rates known from the literature. However, special attention must be paid to the possibility of a selection bias in the different samples. Case series or open studies can therefore easily lead to misinterpretations and are only of limited value. Randomised, control group studies, especially when placebo controlled, are the best basis for statements about the suicide risk of certain antidepressants. But also the results of such control group studies have to be viewed critically under consideration of methodological pitfalls inherent in the design of such trials. For example, most of the respective control group studies on antidepressants do not deal with samples enriched for the symptom suicidality or a risk pattern related to suicidality.

In consequence, data of the most relevant risk groups cannot be recorded during randomised, controlled drug trials. This also holds true for the fact that special risk conditions such as comorbidity, including comorbidity with accentuated personality traits, or even personality disorders, are mostly exclusion criteria in such trials, especially in phase 3 programmes. These comorbidity conditions can increase the risk of suicidality itself, either directly through increased impulsivity or via paradoxical drug effects. Furthermore, during studies careful attention is paid to the early recognition of suicidal crises, which are then immediately compensated for by early intervention, e.g., with additional medication or psychotherapeutic approaches. The chance to prove a negative influence on suicidal behaviour is thus significantly reduced. It should be taken into especial consideration that any negative effect on suicidal behaviour might be of such a small size that it does not reach statistical significance in a trial that was powered for the primary efficacy criterion of an antidepressant trial, i.e., reduction of depressive symptoms.

Due to these limitations of controlled clinical studies, pooled analyses/meta-analyses were applied to improve the chance of detecting a signal about possible effects of antidepressants on suicidality. Other methods of obtaining evidence are required in addition in order to obtain at least a complementary view, such as different kinds of epidemiological analyses, naturalistic follow-up studies, evaluation of complex interventions and also clinical experience with single cases.

Single case experiences are generally seen to be an important possibility to detect suicidality-inducing effects of antidepressants. However, it is important to discuss critically the restricted impact of single case results. For example, single case experiences can only lead to the formulation of a hypothesis, but can never be regarded as giving adequate proof for one. It can only be assumed that there is a 'real finding' if such a hypothesis is validated in a randomised, control-group study or in other kinds of controlled approaches such as quasi-experimental statistical analyses of huge data sets (e.g., epidemiological case control studies). Causal interpretation based on individual case descriptions is extremely prone to false perceptions and bias. Due to the limited amount of theoretical knowledge, the clinician can basically only make vague speculations, which at best can gain support from features of the course of the disorder. The assumption of a causal relationship is mostly based on a temporal relationship between the administration of the antidepressant and the induction/increase of suicidality. However, a series of limitations then have to be imposed in order to put the conclusions into perspective and to avoid one-sided interpretation. The most important points to be considered are listed below:

(a) *Latency periods:* These are important in the evaluation of causal relationships since the conclusions

differ depending upon the estimates of their length. Clinicians are more likely to tend to see a relationship after a relatively short latency period of 1–2 weeks between the commencement of the medication and the occurrence of the event. However, the validity of such a statement is in turn put into perspective, e.g., by the fact that dose increases may, after a certain treatment period, again result in the risk of inducing suicidality.

(b) *Naturalistic course of the depressive episode:* Worsening of a depressive syndrome or suicidality in temporal association with the administration of an antidepressant does not mean that the antidepressant can be accused of being the only cause. It has to be clarified whether the depressive syndrome or suicidality has increased as a part of the natural course of depression. This is particularly relevant in cases when the antidepressant treatment was commenced quite soon after the start of the depressive episode.

(c) *Non-response to antidepressants/chronicity:* If the depression has been present for a longer time these factors can result in increased hopelessness and subsequent suicidality.

(d) *Setting factors:* The organisational setting can also increase depression and/or suicidality. For example, if an inpatient is granted leave from hospital too early on it may over-stress him and result in a worsening of mood. Overburdening may also occur if a patient is treated as an outpatient although inpatient treatment would actually be required due to the severity of his depression or for other reasons.

(e) *Psychosocial factors:* The fact that situational stress factors can intensify an existing depression corresponds to general life experience. Contrary to expectations, psychosocial treatment approaches can worsen depression and cause suicidality [8], at least temporarily, for example if during the therapy topics are addressed that are particularly stressful for the patients or if inexperienced therapists conduct a far-reaching psychotherapy.

(f) *Failure to administer a sedating drug:* The psychopathological picture may change under treatment with antidepressants, either independent of the medication or not, for example in the sense of increased psychomotor agitation and anxiety. In such cases a sedating co-medication or administration of a sedating antidepressant is required, as is the case with primarily agitated, depressed patients with suicidality. A suicidal situation may arise if this rule is not observed.

(g) *Unwanted co-medication effects:* Benzodiazepines, for example, can induce or increase suicidality in rare cases as part of a paradox reaction [5].

(h) *Risk factors:* Irrespective of the type of medication used, certain patients have an increased risk of suicidality for reasons of their family or own medical history, personality traits and comorbidity [9].

Some evidence for a relationship between antidepressant medication and the appearance or increase of suicidality can be hypothetically derived from an alteration of the clinical picture, for example unrest and agitation, soon after administration of the medication, which later results in suicidal thoughts or acts. In contrast, it is also theoretically possible that suicidality can be induced or increased without a change in the psychopathological picture. However, it is then much more difficult to gain at least some hints about possible causal relationships in single case studies. Furthermore, the latency periods to be considered are unclear.

A relatively clear relationship between suicidality and medication can only be proven in single cases if the suicidality subsides after the medication is discontinued, and especially if it increases again after re-exposure. Re-exposure tests, which amount to single case experiments, are not usually conducted for medical/ethical reasons, especially not after such a severe event as suicidality. Another point has to be considered: such a single case experiment may indicate a relevant risk of the antidepressant in a certain person who may have certain predispositions, but does not indicate a general risk.

In the face of all these problems clinical experience from routine daily care, i.e., clinical single case observations, is of limited relevance for the analysis of the effects of antidepressants on suicidality in depressive patients. Such uncontrolled experiences are very error-prone and can therefore only be accepted to a very limited degree as a method of obtaining proof. They should rather be seen as a means of generating a hypothesis, which needs to be confirmed in a type of study that is on a higher methodological level.

Epidemiological studies that analyse the relationship between changes in drug treatment of depression and changes in suicide rates are important as a complementary approach. However, such analyses must take into account several confounding factors that might influence the suicide rate, such as age distribution, alcohol consumption, unemployment rate, etc. Although there might be problems associated with a differentiated interpretation of the results from epidemiological studies in this field, epidemiological methodology has generally reached such an excellent standard that complex statistical analyses taking into account the most relevant confounding factors can generate very reliable results.

However, the situation is quite complex from a pharmacological perspective. For example, the suicide rate has to be seen as a net effect of different pharmacological factors and is not necessarily closely associated with the rate of suicide attempts. If only suicides by drug intoxication are counted, it may be the case, for example, that a highly toxic antidepressant A is characterised by the fact that a high proportion of suicide attempts with this antidepressant

have a fatal outcome. The number of suicides with this drug would thus be highly correlated with the number of times it was used for suicide attempts. The opposite situation is found if an antidepressant B is very safe in case of overdose: the number of suicide attempts with this antidepressant B might not correlate at all with the number of suicides with this drug.

A further pharmacological scenario should be reflected on in this context. Antidepressant A does not increase the rate of suicide attempts, but leads to a fatal outcome (suicide) in case of attempted suicide. Antidepressant B increases the risk of suicide attempts and, although the intoxication with this drug does not have a fatal outcome, it increases the rate of suicide due to the fact that patients use other effective methods to commit suicide. All these aspects have to be taken into consideration. If only suicides with a particular antidepressant are counted, the latter effect of suicide by other means would not be detected.

The situation is obviously already very complex when considering only these pharmacological factors, but it would become even more complex if pharmacological effects not directly but indirectly related to suicidal behaviour were included, for example via effects on impulsivity or aggressiveness [10]. Again, it has to be underlined that behind the net effect on the suicide rate there is a complex system of different pharmacological effects which in the end are related primarily to the following: increase/decrease of suicidal thoughts, increase/decrease of suicide attempts, fatal/non-fatal outcome in case of attempted suicide. This complicated pharmacological background has to be carefully considered when interpreting changes in suicide rate.

Pharmacoepidemiological studies do not connect data on an individual but only on an aggregate level, i.e., national suicide data are analysed in relationship to national antidepressant prescription data, etc. Such studies are also limited to the extent that they can only analyse data on suicides but not on suicide attempts. Clinical cohort studies try to overcome these deficits by assessing the risk of suicidality/suicidal behaviour in cross-sectional analyses of clinical samples and calculating risk figures based on prescription rates of individual antidepressants. Unfortunately, the risk differences found in these studies are often not statistically controlled for confounding factors and can therefore generate misleading results. One such confounding factor is selection bias in prescribing attitudes e.g., in the sense that patients judged as having a higher risk for suicidality are prescribed SSRIs with their known lower fatal toxicity profile. Also, age-related factors might play a role in such a differential prescribing process, e.g., elderly patients might be preferably prescribed SSRIs as they have a better tolerability profile than TCAs. Furthermore, it is well known that elderly patients have a higher risk for suicide. It is difficult to control for all the possible confounding factors, especially if only data from one naturalistic sample are available and if the sample is not large enough to allow analysis of different subgroups with sufficient power. If such studies are not prospective, but retrospective, the *ex post* nature of this approach—the analysis starts with the critical event—might carry the risk of other biases. For example, it is not proven that really all individuals with a critical event are captured from the whole population of treated patients, or whether only a certain (selected) proportion are detected *post hoc*, while others did not show up in the database. Nevertheless, case control studies represent a meaningful approach, if the results are not over interpreted, and are only used for pharmacovigilance purposes, for example. Of especial interest are huge datasets on individual patients that are available from different routine care settings. The cohort of cases showing the unwanted events under certain treatment conditions is controlled in such a case-control study with a random sample of control cases who match patients with respect to psychosocial and other possibly relevant variables, but who are treated differently. However, although the application of sophisticated strategies to control for confounding factors reduces the risk of reaching wrong conclusions, the possibility of severe bias cannot be completely ruled out. For example, in most of these studies differentiated information on psychopathological items such as standardised rating of depression symptoms are lacking. The analysis is therefore mostly restricted to easy-to-collect data like age, gender, etc., which might not be the most relevant risk factors/predictors for the outcome under investigation.

General risk factors [11–14], as well as diagnosis and comorbidity aspects [15–19], should be taken much more into account in studies investigating the risk of increased suicidality under treatment with antidepressants. Consideration of such confounding factors in the calculation can change the risk analysis results significantly, as was shown in several cohort studies [20]. Unfortunately, mostly easily accessible risk factors are considered, while others which require a more sophisticated clinical approach are often neglected. Principally, the aim of these investigations should go beyond the question whether there is a slightly increased risk of suicidality in the whole population treated with antidepressants and should focus much more on the question whether there is a marked risk in a certain subgroup or subgroups.

Even if all relevant confounding factors are taken into account, observational studies are still unable to replace experimental studies in their specific validity. The general limitations of observational studies should be carefully considered. These limitations become primarily apparent in studies determining an association between a treatment and an outcome when the outcome itself is strongly associated with the condition being treated. Confounding by indication, whereby patients are selected for a particular treat-

ment depending upon their diagnosis, the severity of their medical condition or the predicted risk of an unwanted outcome such as suicidality, may lead to erroneous conclusions of a treatment resulting in an adverse outcome [21]. As an example of the differential prescribing pattern, an observational study on 654 anxiety disorder patients [22] should be mentioned. This study found that patients with more suicide risk factors at intake were more likely to be treated with fluoxetine than those without these risk factors.

Hints derived from case reports about a possible suicidality-inducing effect of antidepressants

The available evidence that antidepressants can induce or exacerbate suicidal tendencies primarily comes from case reports. A cluster of these case reports stems from the time after the advent of the SSRIs. In the early 1990s, the discussion whether a certain group of antidepressants might carry certain risks with respect to increasing suicidal ideations/behaviour [5] was stimulated by the case report of Teicher et al. [23], which described the development of "intense, violent suicide preoccupation" in six patients undergoing treatment with the SSRI fluoxetine. According to this report, the patients were so overwhelmed by suicidal ideas that treatment had to be stopped immediately, which in turn led to the resolution of their suicidal crisis after a shorter or longer delay. The authors hypothesised that this might be a specific risk associated with fluoxetine. The paper by Teicher et al. induced others to report similar fluoxetine cases, mostly single patients [24–27]. King et al. [28] reported in a case series about adolescent patients who developed thoughts of self-harm or self-harming behaviour during treatment with fluoxetine. Other SSRIs were also accused in further case reports of having such effects, especially paroxetine in paediatric and adolescent psychiatry [28, 29].

It should be mentioned that not only suicidality but also aggressiveness and other paradoxical effects were reported as case reports in the context of treatment with antidepressants or other psychoactive drugs [5]. Some authors suggested that akathisia, induced by SSRIs, might be a trigger for the induction or worsening of suicidality [27, 30, 31]. Certain subgroups of patients, such as patients with borderline personality disorders, seem to be especially vulnerable to such paradoxical effects [32]. However, also other personality traits or personality disorders may dispose to such paradoxical reactions. It appears that not the most severely depressive patients but those with milder depression have a higher risk of reacting with increased suicidality or paradoxical reactions.

The methodology of case reports in this field, especially that of Teicher et al. [23], was criticised [33, 34] and objections raised to the hypothesised causal relationship in light of the complex clinical situation, which sometimes included co-medication and other predisposing factors. The critical statements made by Miller [33] and Tollefson [34] about Teicher et al.'s case reports [23] give an impression of the methodological problems. The following aspects require consideration in this context:

a. Most patients had previously had suicidal thinking, gestures or attempts.
b. In most patients, it had taken weeks or even months before suicidal ideas disappeared.
c. Most of the patients had been treated earlier or simultaneously with different psychoactive drugs, including benzodiazepines.
d. Some patients had also suffered from suicidal ideations under those antidepressants that had been administered after the withdrawal of fluoxetine.
e. All patients had been non-responders to fluoxetine (and to some other antidepressants!). No case had been reported in which fluoxetine had been able to alleviate the depression.

Due to the pressure of these arguments, Teicher admitted in a Letter to the Editor of the "American Journal of Psychiatry" in 1991 that other antidepressants or other psychotropic drugs e.g., benzodiazapines, possibly through different mechanisms, may also either induce suicidal thoughts or facilitate suicide attempts [35]. Various dispositions and mechanisms have been proposed through which this may occur [32].

Thus, these case reports have to be considered very carefully, also in light of the methodological problems discussed above. The alternative hypothesis that the communication of these extraordinary cases is the result of an observer bias should be taken carefully into account.

Results from pooled analyses of drug company databases

Results of individual antidepressant studies generally delivered no significant indication of increased suicidality [2], which may have been due to the methodological shortcomings mentioned above. Therefore, pooled analyses/meta-analyses were applied to overcome the risk of missing a potential signal.

A pooled analysis of data from 17 randomised, double-blind clinical trials in patients with major depressive disorder comparing fluoxetine (n = 1,765) with a tricyclic antidepressant (n = 731) or placebo (n = 569), or both was performed by Beasley et al. [36].

The results demonstrated that the proportion of completed suicides and suicide attempts in this huge sample was nearly the same in patients treated with fluoxetine as in patients treated with tricyclic antidepressants (in most instances imipramine or amitriptyline). Suicidal acts did not differ at all in the comparison of fluoxetine with placebo (0.2% in each group), and not significantly in the comparison with TCAs (0.7% vs 0.4%, respectively). The pooled incidence of suicidal acts was 0.3% for fluoxetine, 0.2% for placebo and 0.4% for TCAs. These differences were not statistically significant. Suicidal ideation was assessed with item 3 of the Hamilton Rating Scale of Depression (HAMD) [37]. Comparisons of the rating data on suicidal ideation during treatment with fluoxetine and other active drugs failed to demonstrate any tendency towards a higher risk of emergence of substantial suicidal ideas under fluoxetine treatment compared to placebo or the active comparators. The pooled incidence of emergence of substantial suicidal ideation was 1.2% for fluoxetine, 2.6% for placebo and 3.6% for the TCAs. The pooled incidence of worsening of suicidal ideation was similar: 15.3% for fluoxetine, 17.9% for placebo and 16.3% for TCAs.

The authors concluded that the data from the included trials did not indicate that fluoxetine is associated with an increased risk of suicidal acts, or emergence or worsening of substantial suicidal thoughts among depressed patients [36]. The opposite is true, fluoxetine was significantly superior to placebo ($P < 0.001$) in improving suicidal ideation and showed no significant difference to TCAs. The pooled incidence of improvement of suicidal ideation was 72.2% for fluoxetine, 54.8% for placebo and 69.8% for TCAs.

A pooled analysis was also performed on a database of paroxetine studies [38].

Analyses of suicidal thoughts were made on pooled data from all randomised, controlled short-term (up to 6 weeks) efficacy studies of paroxetine. These were all double-blind, parallel-group comparison studies in moderate to severe major depression. Data were available for 2852 patients treated with paroxetine, 554 with placebo and 1101 with reference antidepressants, mostly TCAs. Analysis of suicidal thoughts on the HAMD was carried out on this total database of 4507 patients.

As to the mean scores of the suicide item on the HAMD (a composite of suicidal thoughts and acts), there was no indication of an increase of suicidal thoughts during the trials, either for paroxetine or the active comparators. On the contrary, paroxetine was significantly better than placebo in improving suicidal thoughts at each week measured on all the scales in the different analyses ($P < 0.05$). A similar advantage compared with placebo was seen for the comparator drugs ($P < 0.05$).

In a separate analysis, Montgomery et al. [38] used data from studies in which both the HAMD and the MADRS were applied to investigate emerging suicidal thoughts. Those patients with low scores on the MADRS suicidal thoughts item or the HAMD suicide item were identified.

In this sample, 708 patients treated with paroxetine, 126 treated with placebo and 317 treated with active control had scores of 0 on the HAMD item 3 at baseline. The emergence of suicidality (HAMD item) in these patients was analysed. In the early week 1–2 period there was a significant advantage for paroxetine compared with placebo ($p < 0.05$). In this early period there was no significant difference between active comparators and placebo. There were significantly fewer emergent suicidal thoughts, as measured by the HAMD item 3, in both the paroxetine and active control groups compared with placebo over the 6-week treatment period ($p < 0.01$).

No significant differences were found between paroxetine and active comparators.

In the same paper, Montgomery et al. [38] also published an analysis of the data from the group of controlled studies mentioned above together with data from extensions of controlled studies and open studies.

Among the 4668 patients treated with paroxetine, comparators or placebo in this worldwide clinical trial programme, there were 10 suicides. Calculated per patient year of exposure there were 2.8 times fewer suicides in the paroxetine-treated group compared with active control and 5.6 times fewer compared with placebo. There was no substantive difference between paroxetine and active controls in the incidence of all attempted suicides, including those by overdose, in patients participating in the worldwide paroxetine clinical trials, but there were twice as many attempts per patient year of exposure on placebo compared with paroxetine.

The rate of suicide attempts was lower in the paroxetine-treated group but no significant differences in the number or incidence of attempted suicides (total or by overdose) were found among the paroxetine, placebo and active control groups [38].

A recent meta-analysis of the suicide attempt risk of paroxetine included previously unpublished data [39].

The database for drug registration included 16 placebo-controlled trials, in which 916 patients were treated with paroxetine and 550 with placebo. The number of suicides, suicide attempts and suicidal ideation, reported as side effects, were corrected for duration of medication and the risk was calculated using a standard Bayesian statistical approach with varying priors. There were no suicides. Seven suicide attempts occurred in the paroxetine group and 1 in the placebo group.

Based on the data an increased risk of suicide attempts per year was calculated for paroxetine compared to placebo.

In response to a request by the FDA for data from antidepressant manufacturers for an analysis of adult suicidality data from short-term placebo-controlled trials, the pharmaceutical company GlaxoSmithKline (GSK) conducted a new meta-analysis of suicidal behaviour and ideation in placebo-controlled clinical trials of paroxetine in adult patients with psychiatric disorders, including Major Depressive Disorder (MDD) as well as other depression and non-depression disorders (e.g., dysthymia, panic disorder, generalized anxiety disorder, obsessive compulsive disorder). These trials included 8,958 patients treated with paroxetine and 5,953 with placebo [40].

The results showed a higher frequency of suicidal behaviour in young adults (prospectively defined as age 18–24) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]). This finding was not statistically significant; however, the difference was observed in paroxetine-treated patients with both depressive and non-depressive conditions. In the older age groups (25–64 years and ≥ 65 years), no such increase was observed. Further, in the analysis of adults with MDD (all ages), the frequency of suicidal behaviour was higher in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]). This difference was statistically significant; however, as the absolute

number and incidence of events was small, GSK recommends that these data should be interpreted with caution. All of the reported events of suicidal behaviour in the adult patients with MDD were non-fatal suicide attempts, and the majority of these attempts (8 of 11) were in younger adults aged 18–30. These MDD data suggested that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24. The possible increase in risk of suicidal behaviour in the MDD studies was observed despite substantial evidence for efficacy in the paroxetine-treated patients (compared with placebo) as determined by standardized disease-specific instruments (e.g., HAMD, MADRS). Most patients had an identified social stressor at the time of the event.

GSK summarise that it is difficult to conclude a causal relationship between paroxetine and suicidality due to the small incidence and absolute number of events, the retrospective nature of this meta-analysis, and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves. They state that in their view the overall risk-benefit ratio of paroxetine in the treatment of adult patients with MDD and other non-depressive psychiatric disorders remains positive.

A pooled analysis on suicidality data for the escitalopram database in major depression and anxiety disorders (n = 2,277 for escitalopram; n = 1,814 for placebo) from clinical trials on depression [41] came to the result that the mean value of suicidal thoughts, as measured on item 10 of the MADRS, demonstrated a significant reduction of suicidal thoughts at all time points (weeks 1 through 8, $P < 0.05$ and $P < 0.001$, respectively).

In the analysis of the percentage of patients whose score for suicidal thoughts worsened from baseline to subsequent weeks of treatment during the major depressive disorder trials, there was a numerically lower percentage of patients in the escitalopram group than in the placebo group who reported worsening of suicidal thoughts during treatment. The proportion of suicides or suicide attempts in the whole dataset was extremely low in both groups (around 0.1% in each category in the placebo group, versus no suicides and 0.2% suicide attempts in the escitalopram group).

The pooled analysis of fluoxetine trials performed by Beasley [36] was criticised intensively by Healey and Whitaker [42] under aspects of methodology and decision-making logic. Some of these criticisms are also relevant for the pooled analyses of databases of other SSRIs from other drug companies, and to some extent also for the meta-analyses of drug authority databases. In their paper, Healy and Whitaker criticise several major points.

1. None of the studies in the analysis were designed to test whether fluoxetine could be associated with the emergence of suicidality. All of the fluoxetine studies had been conducted before concerns of suicide induction had arisen. Some of the studies used in the analysis had been rejected by the FDA.
2. Only 3,067 of the approximately 26,000 patients entered into clinical trials of fluoxetine were included in this meta-analysis.
3. No mention was made of the fact that benzodiazepines had been coprescribed in the clinical trial programme to minimize the agitation possibly induced by fluoxetine.
4. No reference was made to the 5% of patients who dropped out because of anxiety and agitation. The 5% dropout rate for agitation or akathisia holds true for other SSRIs as well, and the differences between SSRIs and placebo are statistically significant. Given that the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision* (DSM-IV-TR) has connected akathisia with suicide risk, this point is of importance.
5. This and other analyses depend on item 3 of the HAMD, which can be seen as methodologically unsatisfactory. To claim that the prevention of or reduction of suicidality in some patients in some way means that treatment cannot produce suicidality in others is a logical non sequitur. The argument that item 3 would pick up emergent suicidality in studies run by clinicians who are not aware of this possible adverse effect has no evidence to support it.

Although some of these points are well taken, an over-criticism of these approaches should be avoided. Altogether, the above mentioned pooled analyses of drug companies' data sets on their respective SSRIs failed to demonstrate an increased risk for suicidal behaviour, compared to either placebo conditions or standard comparator drugs. The same is true for the risk of emergent/increasing suicidal ideation. The mean scores of suicidal ideation declined during treatment with SSRIs. Although these analyses appear to have been performed carefully using sophisticated analytical methods, some methodological issues that might have influenced the results can be criticised.

Results of meta-analyses of huge clinical trial databases from national drug authorities and the Cochrane group

Considering the low basal rate of suicidal attempts and especially of completed suicide, one might argue that the database for one individual antidepressant is still too small to have enough statistical power to give an indication of its effects. Following this line of argumentation, meta-analyses based on the huge data sets available to drug authorities might represent a better approach to test the hypothesis of an increased suicide risk associated with SSRIs or antidepressants in general.

Khan et al. [43] assessed suicides, suicide attempts and depressive symptom reduction in the dossiers of 7 new antidepressants available in the Food and Drug Administration (FDA) database. A large proportion of the investigational antidepressants were SSRIs or SSNRIs (venlafaxine), but nefazodone, mirtazapine and buproprion were also included. Imipramine or amitriptyline was mostly used as the active comparator. Most data come from depression studies, but some from preliminary studies in OCD or panic disorders.

Among 19,639 participating patients, 34 committed suicide (0.8% per year), and 130 attempted suicide (2.9% per year). Rates of suicide and attempted suicide did not differ significantly among the placebo- and drug-treated groups. Annual rates of suicide and attempted suicide were 0.4% and 2.7% with placebo, 0.7% and 3.4% with active comparators, and 0.8% and 2.8% with investigational antidepressants, respectively. Reduction of the depression score was 40.7% with investigational drugs (n = 4,510), 41.7% with active comparators (n = 1,416), and 30.9% with placebo (n = 2,805). When considering the results for the individual investigational drugs it becomes apparent that there is a huge variation.

The results of paroxetine are especially impressive; in terms of suicide attempts, paroxetine and its active comparators (4.0% and 5.5%, respectively) appear to have advantages over placebo (8.3%).

In the context of the FDA summary reports, a larger sample of controlled clinical trials (the dossiers for 9 modern FDA-approved antidepressants, including venlafaxine and citalopram) was analysed concerning differences in the suicide rate of SSRIs, standard comparators (mostly tricyclics but also mianserin, mirtazapine, nefazodone, trazodone and maprotiline) and placebo [44].

Of 48,277 depressed patients participating in the trials, 77 committed suicide. Based on patient exposure years, similar suicide rates were seen among those randomly assigned to SSRIs (0.59%, 95% confidence interval [CI] = 0.31–0.87%), standard comparison antidepressants (0.76%, 95% CI = 0.49–1.03%), or placebo (0.45%, 95% CI = 0.01–0.89%).

These findings fail to support either an overall difference in suicide risk between antidepressant- and placebo-treated depressed subjects in controlled trials, or a difference between SSRIs and either other types of antidepressants or placebo [44].

In their paper published in 2003, Healy and Whitaker [42] also criticised the methodology of the earlier analysis reported by Khan et al. [43]. In their view, the calculation of the risk of suicidal behaviour in terms of patient exposure years (PEY) is "inappropriate for the assessment of a problem that clinical studies had clearly linked to the first weeks of active therapy" (48, p. 332). In their view an analysis of suicidal behaviour on the basis of duration of exposure systematically selects patients who do not have the problem under investigation, because those with the problem often drop out of the trial, whereas others who do well are kept on treatment for months or more on grounds of compassionate use [42]. Under consideration of other critical aspects of the Khan study, Healy and Whitaker modified and re-calculated the data presented by Khan et al. [43] in four respects.

1. Suicides and suicidal acts were presented in terms of absolute numbers of patients.
2. On the basis of an FDA paroxetine safety review [45] and FDA statistical reviews on sertraline [46], it became obvious that some of the suicides and suicidal acts categorized as occurring while patients were taking placebo actually occurred during a placebo washout period; placebo and washout suicides were therefore distinguished in the recalculation.
3. Data for citalopram, from another article by Khan et al. [47], were included, although no details about the validity of assignments to placebo were available.
4. Fluoxetine data from public domain documents were presented, again dividing the data into placebo and washout period suicidal acts, along with data for venlafaxine [48].

Based on their re-analysis, Healy and Whitaker [42] came to the following results:

When washout and placebo data were separated and analyzed in terms of suicidal acts per patient (excluding missing bupropion data) using an exact Mantel–Haenszel procedure with a 1-tailed test for significance, the odds ratio of a suicide while taking these new antidepressants as a group (SSRIs, nefazodone, mirtazepine) compared with placebo was 4.40 (95% confidence interval [CI] 1.32-infinity; $p = 0.0125$); the odds ratio for a suicidal act while taking these antidepressants compared with placebo was 2.39 (95% CI 1.66-infinity; $p \leq 0.001$). The odds ratio for a completed suicide while taking an SSRI antidepressant (including venlafaxine) compared with placebo was 2.46 (95% CI 0.71-infinity; $p = 0.16$), and the odds ratio for a suicidal act while taking SSRIs compared with placebo was 2.22 (95% CI 1.47-infinity; $p \leq 0.001$). If washout suicidal acts were included with placebo, as the companies appear to have done, but the denominator adjusted appropriately, the relative risk of suicidal acts while taking sertraline, paroxetine or fluoxetine compared with placebo became significant, with figures ranging from 3.0 for sertraline to over 10.0 for fluoxetine [42].

Unfortunately, Healy and Whitaker [42] did not compare the risk of SSRIs with that of TCAs, which is the most important issue for clinicians' decision-making. Without having access to the original data it is difficult to assess whether these re-calculations are correct. Nevertheless, it is astonishing that the criticised pitfalls were not discussed by Khan et al. in their analyses. On the other side, as the authors suggest, it is not clear that their methodology is principally superior, apart from the differentiation between placebo wash-out and placebo-phase events. For example, it is disputable whether it is adequate to calculate only the numbers of suicidal behaviour events without controlling for the time that the patients are on the active drug or placebo. It is well known that the drop-out rate in the placebo group of such trials is higher than in the active group, thus reducing the time during which a critical event might occur. Thus the methodological approach of Healy and Whitaker [42] does not seem to be beyond critical objections and may be seen to be biased in the other direction.

The pooled analysis performed by Storosum et al. [49] was based on the registration dossiers of antidepressant studies for the indication major depression that were submitted to the Dutch regulatory authorities in the years 1983 to 1997. Attempted and completed suicides were chosen as the outcome criteria.

In 77 short-term studies with 12,246 patients in dossiers from the Medicines Evaluation Board, the incidence of suicide was 0.1% in both placebo groups and active compound groups. The incidence of attempted suicide was 0.4% in both placebo groups and active compound groups. In eight long-term studies with 1,949 patients, the incidence of suicide in the placebo groups was 0.0%, and 0.2% in the active compound groups. Attempted suicide occurred in 0.7% of both placebo groups and active compound groups [49].

The suicide rates of the meta-analysis by Storosum et al. [49] seem to be marginally lower than those found by Khan et al. [43]. This might be due to the more heterogeneous database used by Khan et al., which also included open studies in which 'suicide risk' was probably not an exclusion criterion at entry into the study.

It is regrettable that the data on suicidal behaviour in studies on maintenance therapy or long-term studies are often not published or that the respective information is quite weak, as was also pointed out by Strorosum et al. [49], so that as a consequence those data that are published are quite selective.

In the context of their pooled analysis of registration dossiers described above, Storosum et al. [49] identified by a Medline search all long-term, placebo-controlled antidepressant studies that were conducted in the last decade in patients with major depression and assessed them for attempted suicide. The analysis of this database was unable to demonstrate a significant difference in the risk of suicide attempts between active compounds and placebo. When interpreting the results of the long-term studies it should be considered that even under these long-term conditions (the duration of most of the studies was one year), the basal rate of suicide attempts was low, i.e., up to 0.2%. A similar result was found in an earlier meta-analysis of long-term trial data by Rouillon [50, 51], although there were slight numerical differences favouring the placebo group.

The meta-analysis of SSRI studies in adult patients performed by Gunnell et al. [52] was based on data from the UK regulatory authority.

This huge database included over 40,000 individuals participating in 477 randomised controlled trials comparing SSRIs with placebo. Most trials were performed to assess the efficacy of drugs in the treatment of depression, although trials in other indications such as OCD and anxiety disorders were also included. Sixteen suicides, 172 episodes of non-fatal self-harm and 177 occurrences of suicidal thoughts were reported. Apparently, the data on suicidal thoughts are side-effect related information and not based on rating scales.

The authors found no evidence that SSRIs increased the risk of suicide, but weak evidence of an increased risk of self harm (odds ratio 1.57, confidence interval 0.99–2.55) was found. Risk estimates for suicidal thoughts were compatible with a modest protective or adverse effect (0.77, 0.37–1.55).

The most comprehensive meta-analysis of trial data to date was performed by Fergusson et al. [53], based on a Medline search and on the Cochrane Collaborations register of controlled trials (November 2004) for trials produced by the Cochrane depression, anxiety and neurosis meta-analytical groups.

In order to be included studies had to randomised, controlled trials comparing an SSRI with either placebo or an active, non-SSRI control for any clinical condition (not only for depression!). The latter were divided into the group of tricyclics and the group with therapeutic interventions other than tricyclics – including moclobemide, maprotiline, mianserin and psychotherapy – which is quite an unusual cluster. Seven hundred and two trials with 87,650 patients were primarily included, but only a total of 345 trials representing 36,445 patients reported the numbers of suicidal acts (143 in total) and were included in the analysis. In contrast to traditional terminology, the authors used the term "suicide attempts", including "both fatal and non-fatal acts of suicide". They used their definition of "suicide attempts" as the primary outcome criterion. In addition, they analysed the rates of "fatal" and "non-fatal" suicide attempts separately. A significant increase in the odds ratio of suicide attempts (odds ratio 2.28, 95% confidence interval 1.14 to 4.55, number needed to treat to harm 684, $p = 0.02$) was observed for patients receiving SSRIs compared with placebo. Given the reduced sample sizes, the ability to detect significant differences within subgroups was limited. In the comparison of "non-fatal suicide attempts", a significant difference overall remained (2.70, 1.22 to 5.97; $p = 0.001$). In the comparison of "fatal suicide attempts", no difference was detected between SSRIs and placebo (0.95, 0.24 to 3.78). In the pooled analysis of SSRIs versus tricyclic antidepressants, no difference in the odds ratio of "suicide attempts" (0.88, 0.54 to 1.42) was detected. The odds ratio of "non-fatal suicide attempts" for SSRIs compared with tricyclic antidepressants was 0.85 (0.51 to 1.43) and the odds ratio of "fatal suicide attempts" was 1.08 (0.28 to 4.09). The value of 7.27 (1.26 to 42.03) given in the original publication as the odds ratio of "fatal suicide attempts" was later corrected by the authors [54].

There was an increase in the odds ratio of suicide attempts when comparing SSRIs with therapeutic interventions other than tricyclic antidepressants (1.94, 1.06–3.57, number needed to treat to harm 239). The respective odds ratio for "fatal suicide attempts" was 0.59 (0.16–2.24) and that for "non-fatal suicide attempts" 2.25 (1.16–4.35) [53].

Because this meta-analysis attracted a lot of attention, it deserves more detailed consideration. The authors' conclusion that there is an association between "suicide attempts" and the use of SSRIs becomes an important population health issue and should be extended to the TCAs, based on the findings that there was no difference between SSRIs and TCAs in the odds ratio for "suicide attempts". In the discussion section of their paper, the authors focus on their finding of a more than twofold "increased rate of suicide attempts" (defined according to their unusual terminology as including both suicide and suicide attempts) with SSRIs compared to placebo. They also underline that they found a difference in absolute risk of 5.6 suicide attempts per 1,000 patient years of SSRI exposure compared with placebo. "Although small, the incremental risk remains a very important population health issue because of the widespread use of SSRIs." (22, p. 398). Interestingly, although they state that they found no significant difference between SSRIs and tricyclic antidepressants, they do not discuss this very important finding. Apparently, they were no longer interested in the question whether the described effect of SSRIs is specific to this pharmacological class of antidepressants or whether it is related to all antidepressants and includes the tricyclics, although they investigated this question in their analyses.

Fergusson et al. [53] underline the finding that the relative increase of "suicide attempts", according to their terminology, during SSRI treatment versus placebo was restricted to "non-fatal suicide attempts", and did not include "fatal suicide attempts", which is a very important differentiation. They discuss several reasons for this result, such as type and severity of depression and a different risk pattern in patients with less severe clinical conditions for SSRI-induced agitation/akathisia. Altogether, these are mostly speculations not based directly on the results of the meta-analysis. Of interest in this context is the finding mentioned in the discussion of the study that estimates for patients with major depression indicated a decrease in "suicides" with SSRIs, whereas both patients with other types of depression and those with other clinical indications may have as much as an eightfold increase in their rates of suicide, thus

resulting in an overall null effect. From a clinical standpoint, it would be very important to know whether the risk ratios for "suicide attempts" and "non-fatal suicide attempts" follow a similar pattern or whether there are differences, e.g., between those in drug trials on depression and those in drug trials in other indications like anxiety disorders. The text of the publication does not clarify this. Figure 2 of the publication gives the impression that numerically there is no difference between the three subgroups "major depression", "depression" and "other conditions" in terms of "suicide attempts". This is of special interest to the extent that meta-analytical results from SSRI studies in child and adolescent psychiatry show an increased risk of suicidal thoughts and suicide attempts, especially in the subgroup of patients suffering from psychiatric conditions other than depression [55].

Altogether the results of these meta-analyses show a certain consistency to the extent that most of them did not find any differences between the risk of suicidal behaviour under modern antidepressants/SSRIs compared to placebo conditions or treatment with standard antidepressants, mostly TCAs. However, in the meta-analysis by Fergusson et al. [53], which included the largest number of studies, an approximately twofold increased risk of suicidal behaviour (suicide and suicide attempts) was seen when SSRIs were compared with placebo. The increased risk found in the primary outcome measure of this meta-analysis was explained by a higher risk of suicide attempts, while there was no increased suicide risk.

Unlike the other meta-analyses, Fergusson et al. [53] found no difference between SSRIs and TCAs with respect to the risk for suicidal behaviour. It could be speculated that the significant results found by Fergusson et al., which contrast those of the other meta-analyses, could be due to the greater sample size. In this context it should be mentioned that also the other relatively large meta-analysis, by Gunnell et al. [52], found some indication ("weak evidence") that SSRIs could induce a risk of suicide attempts. Another reason for the different finding could be the inclusion of a greater number of antidepressant trials in indications other than depression. Interestingly, Fergusson et al. found in a subanalysis that there were some differences between major depression and other depressions or other indications in terms of suicide risk.

In some of these meta-analyses there is a numerical but not statistically significant disadvantage for SSRIs in terms of risk of suicidal behaviour, which, as described above, reached statistical significance in the study by Fergusson et al. [53]. Could this be due to a methodological artefact? In placebo-controlled studies, the designer of the protocol and/or the physicians performing the study have the strong tendency not to include suicidal patients and/or to exclude them as early as possible if the patient's condition worsens during the study. This might result in a lower rate of suicidal behaviour in the placebo-controlled trials. This effect of lowering the risk for suicidal behaviour is not present in active comparator studies. If placebo-controlled and active comparator studies are pooled for meta-analyses, the higher risk of suicidal behaviour in the latter studies could result in SSRIs and/or TCAs appearing to have a higher risk compared to placebo. To avoid this bias, conclusions in this respect should be primarily based only on the placebo-controlled studies, or this effect should at least be controlled for in pooled analyses that mix both types of studies.

Taking into account alternative explanations, the more general question should be discussed whether the low risk of suicidal behaviour in the placebo groups might to some degree be a consequence of the fact that in these groups 'overdose' is often not detected as such because there are no medical consequences. This might be an important issue at least with respect to events in which the method of deliberate self-harm is identical to the medication in the respective trial arm.

Evidence from pharmacoepidemiological and cohort studies

It was discussed above that due to the inherent methodological limitations of the available randomised controlled efficacy studies, other, complementary scientific approaches should be used to answer the question of a potentially increased risk of suicidal behaviour with SSRIs or other antidepressants.

Pharmacoepidemiological studies, which analyse the relationship between changes in the drug treatment of depression and changes in suicide rates, are important as such a complementary approach. Several pharmacoepidemiological studies reported a decline of the suicide risk associated with an increased prescription rate of antidepressants. In these studies, there was no hint of an increased risk of suicide associated with the increased prescription rate of SSRIs, which have become more and more widely used over the last 10–15 years [2]. Analyses that took into account possible confounding factors such as changes in age distribution, unemployment rate, alcohol consumption, etc., did not reach any different conclusions [7, 56–61]. However, these results cannot rule out the possibility of an increased risk of suicide attempts due to SSRIs or other antidepressants. They also cannot rule out a risk for suicidal behaviour in a few individuals with idiosyncratic risk profiles.

These pharmacoepidemiological studies do not connect data on an individual but only on an aggregate level, i.e., national suicide data are analysed in relationship to national antidepressant prescription data, etc. They are also limited to the extent that they can only analyse data on suicides but not on suicide attempts. Clinical cohort studies try to overcome

these deficits by assessing the risk of suicidality/suicidal behaviour in cross-sectional analysis of clinical samples and calculating risk figures based on prescription rates of individual antidepressants.

Fava and Rosenbaum [62] published a survey of 27 psychiatrists who treated 1017 depressed outpatient with antidepressants during 1989: 3.5% (8/231) of those treated with fluoxetine alone, 6.5% (4/62) of those treated with fluoxetine and tricyclics, 1.3% (5/385) of those treated with tricyclics alone or with lithium, and 3.0% (3/101) of those treated with other antidepressants became suicidal after treatment with these antidepressants was initiated. The study failed to find an association between monotherapy with fluoxetine and suicidal ideation/behaviour. If one would like to draw any conclusion from this study's naturalistic data, it could be that those who needed comedication of fluoxetine and TCAs demonstrated a risk of suicidality, while the risk in monotherapy with fluoxetine or TCAs was similar. These results may have possibly been due to a selection of patients or to certain pharmacodynamic interactions.

More comprehensive studies of suicidal behaviour were based on the General Practice Research Database in the UK. The first study compared the risk of suicide in people taking antidepressants commonly prescribed between 1988 and 1993 [63].

The authors reported 143 suicides among 172,598 patients taking antidepressants and found a statistically significant doubling of the relative risk of suicide with fluoxetine compared with the reference antidepressant, dothiepin, when calculated in terms of patient exposure years. Controlling for confounding factors such as age, sex and previous suicide attempts left the relative risk at 2.1 times greater for fluoxetine than for dothiepin and greater than any other antidepressant studied, although statistical significance was lost in the process.

Although this study found some evidence of an increased risk of suicide among people prescribed fluoxetine, it was difficult to interpret because the drug's safety in overdose may have led to selective prescription to people at risk of self harm.

In a subsequent study, Jick et al. [64] compared the risks for suicide and non-fatal suicidal behaviour between 159,810 people prescribed fluoxetine, paroxetine, amitriptyline, and dothiepin in 1993–1999. The study was not restricted to patients prescribed antidepressants for the treatment of depression. No notable differences were found between the drugs with respect to risk for fatal or non-fatal suicidal behaviour.

A recent nested case-control study, based on the General Practice Research Database, of patients with a new diagnosis of depression who were prescribed antidepressants for the first time between 1995 and 2001 was published by Martinez et al. [65]. This study compared the risk of non-fatal self harm and suicide in association with the use of SSRIs and tricyclic antidepressants.

1968 cases of non-fatal self harm and 69 suicides occurred. The overall adjusted odds ratio of non-fatal self harm was 0.99 (95% confidence interval 0.86 to 1.14) and that of suicide 0.57 (0.26 to 1.25) in people prescribed SSRIs compared with those prescribed tricyclic antidepressants. Little evidence was found that associations differed over time since starting or stopping treatment. Some evidence was found that risks of non-fatal self harm in people prescribed SSRIs compared with those prescribed tricyclic antidepressants differed by age group (interaction $p = 0.02$). The adjusted odds ratio of non-fatal self harm for people prescribed SSRIs compared with users of tricylic antidepressants for those aged 18 or younger was 1.59 (1.01 to 2.50), but no association was apparent in other age groups. No suicides occurred in those aged 18 or below currently or recently prescribed tricyclic antidepressants or SSRIs [65].

The principal methodological aspects mentioned above make it difficult to draw robust conclusions from these findings.

Leon et al. [66] reported on data from the National Institute of Mental Health Collaborative Depression Study, a prospective, naturalistic follow-up of persons who presented for treatment of affective disorders.

The analyses included data on 643 subjects. Nearly 30% ($N = 185$) of the study group was treated with fluoxetine at some point during the follow-up period. Relative to the other subjects, those who were subsequently treated with fluoxetine had an onset of affective illness at a younger age and, after intake into the study and before 1988, had elevated rates of suicide attempts before fluoxetine treatment. A mixed-effects survival analysis that incorporated treatment exposure time, multiple treatment trials and multiple suicide attempts per subject showed that relative to no treatment, use of fluoxetine and use of other antidepressants were associated with non-significant reductions in the likelihood of suicide attempts or completions. Severity of psychopathology was strongly associated with elevated risk, and each suicide attempt after intake into the Collaborative Depression Study was associated with a marginally significant increase in risk of suicidal behaviour.

The results did not support the hypothesis that fluoxetine increases the risk of suicide. Rather, there was a nonsignificant reduction in risk of suicidal behaviour among patients treated with fluoxetine, even though those subjects were more severely ill before treatment with fluoxetine [66].

Donovan et al. [67] presented data on 222 suicides, collected over the period 1990–1994 in the UK.

Forty one (18.5%) of the cases had been prescribed one antidepressant within one month of their suicide. The ratio between the occurrence of suicide and the prescription of different classes of antidepressant, particularly TCAs and SSRIs, indicated that suicide by any method (violence, gassing, poisoning by ingestion of any substance) was more likely to occur following the prescription of SSRIs than of TCAs. They found some evidence that less-overdose-toxic antidepressants were preferentially prescribed to patients at a higher risk of suicide, and assumed that this largely explained their finding.

They concluded that whilst preferential prescribing of safer-in-overdose antidepressants will reduce fatalities due to TCA overdose, this tactic is unlikely, by itself, to have a significant effect on the overall suicide rate.

In a later publication, Donovan et al. [68] reported on a further epidemiological study on 2,776 acts of deliberate self-harm (DSH).

This was a prospective, observational, cross-sectional study of all consecutive cases of DSH, aged 17 years or over, who attended the accident and emergency (A&E) department of the Derbyshire Royal Infirmary as a consequence of any act of DSH during the 2-year

period between 1 January 1995 and 31 December 1996. Data about each case were collected from two sources: demographic and DSH event-specific data were recorded from A&E attendance records, and data about antidepressants prescribed for depressive symptoms before the DSH event were collected from primary care records via a postal questionnaire to the general practitioner. The number of prescriptions written for antidepressant drugs in the Southern Derbyshire Health Authority region (from Prescribing Analysis and Cost (PACT) data) during the time of the study was used to calculate the incidence of DSH, expressed as number of DSH cases per 10 000 prescriptions, for different antidepressant drugs. The relative incidence of overdose with SSRIs was greater than that with TCAs (16.0 *v.* 11.8 cases per 10 000 prescriptions respectively). This pharmacological class finding was strongly influenced by the SSRI fluoxetine, for which the relative incidence of overdose was significantly greater than that for the TCAs amitriptyline, imipramine and dothiepin (19.4 *v.* 11.4 *v.* 9.8 *v.* 6.9 cases per 10 000 prescriptions respectively; $P < 0.001$). Pairwise comparisons of the relative incidence of DSH by any method following the prescription of named antidepressant drugs within 30 days prior to the DSH event indicated that the relative incidence of any DSH event in patients who were prescribed the SSRIs fluoxetine, paroxetine and sertraline (19.8, 12.1 and 14.8 DSH events per 10 000 prescriptions respectively) was significantly higher than that in patients prescribed the TCAs amitriptyline, dothiepin and imipramine (3.0, 4.1 and 3.5 DSH events per 10 000 prescriptions respectively; $P < 0.001$). It is important to appreciate the distinction between the risks associated with antidepressant overdose and the risk of any form of DSH during treatment with antidepressants at therapeutic doses. In the present study, less than one-third of DSH cases who had been prescribed an antidepressant overdosed on that antidepressant. The majority of DSH cases who had been prescribed an antidepressant harmed themselves by means other than antidepressant overdose.

The finding in this study that the morbidity after TCA overdose, measured in terms of the duration of stay in hospital to effect recovery, is greater than that seen after overdose with SSRIs is not surprising, given the known difference in the overdose toxicities of these two classes of antidepressant [69]. However, this study has also indicated that the risk of DSH by any method is greater in patients who had been prescribed an SSRI than in those who had been prescribed a TCA prior to the DSH event. There are a number of factors which may have influenced the findings from this study. Furthermore, the fact that this is an observational cross-sectional study rather than a randomised controlled trial leads to the question whether patients prescribed TCAs were similar in terms of DSH risk to those prescribed SSRIs. Each of these limitations weakens the conclusions that can be drawn from this study, although some of the uncontrolled DSH risk factors can be examined to estimate the likelihood of their effect on the result. There are a number of other possible factors which may have influenced the result but which are beyond the scope of exploration from the study database. These unaccountable factors include: the clinician's personal judgement of risk of DSH at the time of prescription regardless of previous DSH history; differences in the compliance of patients to taking TCAs or SSRIs; differences in efficacy and/or tolerability of TCAs and SSRIs in a routine primary care setting (as opposed to a clinical trial); differences in severity of depressive illness in those prescribed TCAs or SSRIs; differences in antidepressant prescription frequency for conditions other than depressive illness (e.g., chronic pain, enuresis, obsessive-compulsive disorder, weight management) which may affect the denominator (total number of prescriptions) for the relative incidence calculations to different degrees for different antidepressants; and a pharmacological effect of increased suicidality in susceptible individuals [68].

Another cohort study was performed in New Zealand [20], following a retrospective, nested case control design.

A total of 57,361 patients who received a prescription for a single antidepressant were identified from a nonrandom sample of general practices from 1996 to 2001. Suicides and self-harm events within 120 days of a prescription were identified from the New Zealand Mortality Database and the New Zealand Hospital discharge database, respectively. Twenty-six suicides and 330 episodes of self-harm were identified within 120 days of an antidepressant prescription. On univariate analysis the association, expressed as OR (95% CI), between selective serotonin reuptake inhibitors (SSRIs) and self harm and suicide were 2.26 (1.27–4.76) and 1.92 (0.77–4.83), respectively. When corrected for the confounding effects of age, gender and depression/suicidal ideation there was an association between SSRIs and self harm, OR 1.66 (95% CI 1.23–2.23), but not for suicide, 1.28 (0.38–4.35).

In the discussion of these results, the authors underline the principal limitations of observational studies in determining an association between a treatment and an outcome, and its potential causal background. Based on the modification of the primary results after inclusion of the potential confounders, they conclude that factors such as age, gender, depression and suicidal ideation are the primary risk factors for the outcome results. They interpret these results with the hypothesis that doctors preferentially prescribe SSRIs to patients with a greater risk of suicide or self-harm while TCAs are prescribed to patients without depression necessarily being the indication.

The study by Simon et al. [70] was induced by the recent FDA warnings about potential suicidality-inducing effects of antidepressants. The authors used population-based data to evaluate the risk of suicide and serious suicide attempts in relation to the initiation of antidepressant treatment.

Computerized health plan records were used to identify 65,103 patients with 82,285 episodes of antidepressant treatment between January 1, 1992, and June 30, 2003. Death by suicide was identified by using state and national death certificate data. Serious suicide attempt (suicide attempt leading to hospitalization) was identified by using hospital discharge data. In the 6 months after the index prescription of antidepressant treatment, 31 suicide deaths (40 per 100,000 treatment episodes) and 76 serious suicide attempts (93 per 100,000) were identified in the study group.

The risk of suicide attempt was 314 per 100,000 in children and adolescents, compared to 78 per 100,000 in adults. The risk of death by suicide was not significantly higher in the month after starting medication than in subsequent months. The risk of suicide attempt was highest in the month before starting antidepressant treatment and declined progressively after starting medication. When the 10 newer antidepressants included in the FDA warning were

compared to older drugs, an increase in risk after starting treatment was seen only for the older drugs.

Mackay et al. [71] published tolerability data from four observational cohort studies on fluvoxamine, fluoxetine, sertraline and paroxetine. The data were collected immediately after release of each of these antidepressants by the Presciption Pricing Authority in England. Each of the four groups exceeded 10,000 patients. No difference was found in terms of suicide, which amounted to 0.2% for all drugs, apart from paroxetine with 0.3%.

Results of a cohort study performed in Finland were presented at the 19th ECNP congress, September 2006 [71a]. In order to elucidate the connection between SSRIs and suicide, the investigators studied people who had been hospitalized for attempted suicide and were thus at high risk for attempting suicide.

They collected data from 3 large Finnish databases (National Hospital Registry, National Prescription Registry, and National Mortality Registry) on 15,390 individuals who had been hospitalized for any reason. The follow-up data consisted of 152,587 person-years. A total of 7136 patients were identified who had been hospitalized for attempted suicide and 602 who had died by suicide; 1583 of the patients who had attempted suicide eventually died from other causes.

In the initial analyses, all classes of antidepressants were associated with an increased risk of suicide: tricyclics, SSRIs and SNRIs ($P < 0.001$ for each drug class). However, when medication use was adjusted as a time-dependent variable, the association was not statistically significant and treated patients were found to be less likely to complete suicide. Furthermore, some preliminary evidence showed that untreated patients were more likely to use violent means, such as shooting or hanging. Of interest was that those receiving SSRIs were less likely to die of cardiovascular or cerebrovascular causes (relative risk, 0.59; $P < 0.001$).

To summarise, pharmacoepidemiological studies that investigate the association between the prescription risks for TCAs/SSRIs and suicide rates by applying sophisticated statistical methods show no increased risk of suicide in association with antidepressants, especially no increase of suicide risk in conjunction with SSRIs. The opposite is true [2], two naturalistic cross-sectional [64, 65] and one naturalistic follow-up study [66] on clinical samples were not able to find differences between SSRIs and TCAs in terms of suicidality, suicide attempts or suicide. Another cross-sectional naturalistic study on a clinical sample found some differences to the disadvantage of SSRIs [63], but after controlling for confounding factors the difference was no longer significant. Two other cohort studies [20, 68] suggested that patients treated with SSRIs demonstrate a higher risk of self-harm. Didham et al. [20] suggested that this outcome might be related to a differential prescribing pattern and not to the drugs themselves. It should also be considered that in the study by Donovan et al. [68], patients treated with TCAs and taking an overdose of these drugs had more medical complications (longer hospital stay) than those with an SSRI intoxication. It should be noted that confounding factors were not controlled for in the study by Donovan et al. [68], while the control for some confounding factors in the study by Didham et al. [20] reduced the increased risk substantially. This led Didham to conclude that the risk is potentially not a certain drug itself, but the preferential use of a certain drug in patients at risk. The study by Simon et al. [70] suggested advantages of antidepressant treatment compared to the preceding non-treatment phase and a reduction of risk with newer antidepressants compared to TCAs.

Toxicity of the TCAs

A critical factor is surprisingly more or less ignored in the current risk/benefit discussions about antidepressants and suicidality: the overdose safety of antidepressants [72]. Consumption of a 1 or 2 week's dose of a TCA with the intention of committing suicide can be fatal, while patients normally survive an overdose even with excessively high doses of SSRIs or other newer antidepressants without any consequences. This has been demonstrated in numerous studies. Whyte [73] showed that the risk of falling into coma or requiring intensive medical care after attempting suicide with TCAs was disproportionately higher than with SSRIs. Patients first admitted for deliberate self-poisoning with antidepressants to a toxicology unit were included in the study. 17.7% of the patients with TCA poisoning were comatose, compared to only 1.3% of those with SSRI poisoning. 45.9% of the 172 patients with TCA poisoning required treatment in intensive care, compared to only 7.3% of the 233 patients with SSRI poisoning.

A study from England estimates that more than 300 deaths by suicide a year result from intoxication with TCAs [74].

Between 1997 and 1999 there were 233,756 hospital admissions for overdose, 1,149 (0.5%) of these ended in the death of the patient. Such deaths accounted for 28% of all overdose suicides and 8% of total suicides. The median time between admission and death was three days (interquartile range one to nine days). The most commonly identified drugs taken in fatal overdose were paracetamol compounds, benzodiazepines and tricyclic/tetracyclic antidepressants.

A health economical study estimated that in England 300–450 deaths by overdose could be prevented by prescribing SSRIs instead of TCAs [75].

Some research in this field has tried to evaluate the risk of fatal outcome in case of intoxication with individual antidepressants. This was performed by analysing the association between annual national death rates due to intoxication with antidepressants and annual national prescribing/selling rates of individual antidepressants. Several authors have presented the mortality statistics for antidepressants and

calculated indices to determine the relative toxicity of different medications. Their calculations were based on the number of deaths either per kilogram of a drug or per million defined daily doses (standard quantity units) prescribed [69, 76–79]. Additionally, the fatal toxicity index (FTI) was defined as the number of deaths caused by an antidepressant divided by the number of prescriptions (in millions) of this drug during a given period of time. The FTI has been shown to be significantly higher for TCAs than for the SSRIs [69, 80], leading the authors to conclude that switching to medications with a low index would reduce the number of lethal incidents [81].

This approach was primarily used by Henry and Cassidy in several studies of different time periods in the UK [69, 76, 78]. The general result of these studies was that second generation antidepressants, including mianserin and the SSRIs, are associated with a lower rate of fatal outcome. This was interpreted as indicating a lower toxicity of modern antidepressants. It should be noted that these kinds of studies do not investigate the general risk of suicidal behaviour, but only the fatal risk for those who died in connection with an overdose of an antidepressant. In their study published in 1995 [69], Henry et al. reported that the mean annual number of deaths due to overdose with a single antidepressant over the six years was 268 (range 238–288). The tricyclic drugs were implicated in most deaths, with two drugs—amitriptyline and dothiepin—accounting for 81.6% of all deaths. The tricyclic antidepressants as a group had a significantly higher number of deaths per million prescriptions than expected compared with all the antidepressants taken together ($P < 0.001$). The monoamine oxidase inhibitors as a group had a lower than expected number of deaths per million prescriptions ($P < 0.001$). The groups of atypical antidepressants and selective serotonin reuptake inhibitors each had the lowest number of deaths per million prescriptions ($P < 0.001$). Three of the tricyclic agents (dothiepin, amitriptyline and amoxapine) had a significantly higher number of deaths per million prescriptions than expected. A further three drugs from this group (lofepramine, clomipramine and trimipramine) had a significantly lower number of deaths per million prescriptions than expected when compared with all antidepressants. One monoamine oxidase inhibitor (phenelzine) had a significantly lower number of deaths per million prescriptions. Two of the atypical drugs (mianserin and trazodone) had a significantly lower number of deaths per million prescriptions. Three of the selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, and paroxetine) had a lower number of deaths per million prescriptions. No deaths were recorded for five drugs, all of which had low prescription figures. Calculation of data with defined daily doses showed a pattern that was broadly similar to the data derived from deaths per million prescriptions [69]. A more recent study [82] using a new database of deaths from overdose and poisoning in England and Wales between 1993 and 1997 supported the view that in overdose newer antidepressants are less toxic than TCAs.

A study based on data from the Institute of Forensic Medicine, University of Vienna, Austria, confirmed the lower toxicity risk of SSRIs [81, 83].

Fatal poisonings were ranked based on the *f*-value of each single substance. In relation to the toxicity rate of all antidepressants prescribed (f^{all}_{mono}= 0.7), the TCAs doxepine (f_{mono} = 4.3), dibenzepine (f_{mono} = 2.8) and amitriptyline (f_{mono} = 1.7) were associated with a significantly higher value, while that of citalopram (f_{mono} = 0) was significantly lower. Compared to the SSRI-group (f_{mono} = 0), the antidepressants of the TCA-group showed a significantly higher *f*-value (f_{mono} = 1.3). Frey et al. also analysed intoxications by a combination of substances (poly) as well as the total of single- and poly-substance intoxications (total). As in single-substance intoxications, the f_{poly}-values of doxepin and amitriptyline were again significantly higher than the index calculated for all antidepressants involved in poly-substance intoxications (f^{all}_{poly}= 3.6). Significantly lower f_{poly}-values were found for citalopram, fluoxetine, paroxetine, moclobemide and opipramole. The f_{poly} value of 6.3 calculated for TCAs is in sharp contrast to the f_{poly}-values obtained for MAOIs ($P \leq 0.05$) and SSRIs ($P \leq 0.001$), which range from 0 to 0.3.

Without going into further details of this complex analysis, it can be summarised that TCAs turned out to be more toxic than SSRIs and other novel antidepressants.

Although this information might be helpful in the choice of antidepressants, several questions remain about the profile of toxicity of different antidepressants, e.g., among others it should be examined whether certain antidepressant drugs are more likely to be used in multiple drug overdoses, particularly in combination with other antidepressants or other psychoactive drugs. A recent study of this type tried to overcome these problems by assessing the relative toxicity of the major classes of antidepressants in relation to the cause of death [84].

The study population consisted of cases reported by coroners in England and Wales to the National Programme of Substance Abuse Deaths (np-SAD; established in 1997 after the Home Office's index of addicts closed; [85]) for deaths occurring during the 3-year period 1998–2000. Cases for the study were those who had a current prescription for antidepressant drugs at the time of the fatality and where antidepressant drugs were implicated in the cause of death. Most deaths from antidepressant drugs were suicides (80%). Tricyclic antidepressants (TCAs) accounted for more drug mentions than did other antidepressant drugs (12 per million prescriptions). SSRIs were associated with a significantly lower risk of toxicity, and 93% of deaths from SSRIs occurred in combination with other drugs, especially TCAs (24.5%).

In 'combination' deaths patients were significantly more likely to have had a history of drug misuse. Finally, the study suggests that, of the miscellaneous group of antidepressants, venlafaxine may be more toxic in overdose than other drugs from the group of SSRIs.

These results are also supported by a study from the USA [86].

In this study, information regarding suicide attempts and suicides by antidepressant overdose was obtained from the published reports of the Drug Abuse and Warning Network and the annual report of the American Association of Poison Control Centers, and corrected for differences in total annual prescriptions using data

from the National Prescription Audit. The risk of a suicide attempt did not appear to differ among antidepressants, but the tricyclic antidepressants were associated with a higher rate of death in the event of an overdose than the newer nontricyclic antidepressants in both the annual report of the American Association of Poison Control Centers and the Drug Abuse and Warning Network data [86].

Similar results were also obtained from Sweden [87].

Detections of different antidepressants in the forensic toxicological screening of 14,857 suicides were compared with those in 26,422 cases of deaths by accident or natural causes in Sweden 1992–2000. There were 3,411 detections of antidepressants in the suicides and 1,538 in the controls. SSRIs had lower odds ratios than the other antidepressants. In the 52 suicides under 15 years, no SSRIs were detected, and in 15–19-year age group, SSRIs had lower relative risk in suicides compared with non-SSRIs [87].

Bateman et al. [88] analysed overdose admissions in relation to prescribing rates in Edinburgh. They found no clear distinction between TCAs and newer antidepressants. Altogether, amitriptyline- and sertraline-treated patients were slightly underrepresented, while mirtazapine, trazadone and venlafaxine patients were more or less overrepresented. There was no evidence of an excess likelihood for overdose with SSRIs, and also not for TCAs.

To summarise this subchapter: there is strong evidence for a higher fatal toxicity of TCAs compared to SSRIs and some other modern antidepressants in most of the studies.

The suicidality-inducing risk of antidepressants/SSRIs in children/adolescents: recent data

Various national drug regulatory authorities such as the British Medicines and Healthcare Products Regulatory Agency (MHRA) and the American Food and Drug Administration (FDA) warned in recent years that induction of suicidality should be seen as a serious side effect of SSRIs in children and adolescents, and that it should therefore be considered extremely carefully whether SSRIs or rather other treatment approaches are indicated in depressive children or those suffering from compulsive disorders. The licensing authorities formulated their statements somewhat differently and also specified somewhat different conditions. However, the principal message remains the same [89]. In anticipation of upcoming data, especially the results of several meta-analyses, several more general articles in the field of child and adolescent have warned that caution should be applied when prescribing SSRIs and other antidepressants to children and adolescents [90–94].

As this review focuses on adult psychiatry, the respective findings from child/adolescent psychiatry will be mentioned only briefly. On the other side, it seems necessary to include these findings in the argumentation of this paper because they can potentially add some complementary aspects to the whole issue.

As in adult psychiatry, concerns about suicidality-inducing effects of SSRIs in children and adolescents were first expressed in case reports [28, 29].

According to the review performed by Vitiello and Swedo [95], the data that formed the basis for the registration of various SSRIs and were obtained from controlled studies performed in child and adolescent psychiatry do not allow any statistically significant conclusions to be drawn, either for an individual drug or overall. At the most a numeric difference can be determined, although this is on a very low level (3.7% in the active substance group and 2.5% in the placebo group). In this context it is also of interest that of the 4,100 children and adolescents included in the SSRI studies, not one committed suicide [95].

A meta-analysis [55] of 6 placebo-controlled SSRI studies in children and adolescents published in 1994 or earlier showed no significant differences between SSRIs and placebo with respect to the frequency of suicidal thoughts and attempts and self-endangering behaviour ($0.21 < P < 1.0$). There was no completed suicide in any of the studies.

The explorative analysis of the pooled data from 951 participants of all 6 studies yielded no clear indication of increased suicidality during treatment with SSRIs, although suicide was observed more frequently under the active substance than under placebo (2.1% vs 0.8%; relative risk 2.46; $p = 0.11$). The highest relative risks for suicidality were found under paroxetine (4.68; $p = 0.21$) and sertraline (2.47; $p = 0.45$). The meta-analysis of the data from the 6 studies showed a non-significant medial effect size with respect to suicidality that was close to zero ($D = -0.06$, $t = -1.52$, $p = 0.19$), and very homogenous study effects ($\chi^2 = 1.05$, $p = 0.96$).

A study recently performed in Sweden allows the risk that SSRIs carry with respect to suicidality to be estimated [87]. In Sweden the medication taken by anyone who took their own life was systematically analysed over many years.

In the age group up to 14 there were 52 suicides. Antidepressants were detectable in 5 of these suicide victims, but none of these was an SSRI, even though these are the most frequently prescribed antidepressants in this age group (80%). In the 15- to 19-year-old age group, SSRIs had a lower relative risk of inducing suicide compared with other antidepressants.

Although this is an important study, it cannot rule out the possibility that SSRIs trigger suicidal behaviour in general, and even suicide attempts with fatal outcome performed with drugs other than antidepressants or by other methods, and can therefore only partially contribute to answering the question at hand.

Gunnell and Ashby [96] summarised the evidence from clinical trials on the adverse effects of SSRIs on suicidal behaviour in children, abstracted from information released by the MHRA. No suicides occurred in these trials. The pooled estimate of increased risk of suicidal thoughts or behaviour from these data was 1.66 (95% confidence interval 0.83–3.50). The authors advised to interpret this apparent increase in risk with caution since people taking

SSRIs may be more likely to report adverse effects, perhaps because the drugs could have a disinhibiting effect. In addition, response to treatment may lead to reactivation among people whose depression previously prevented them from acting on suicidal impulses [97]. Furthermore, any increased risk may be counterbalanced by a longer term reduction in suicidal behaviour; such benefits would not be detected in the trials as they generally lasted 10 weeks or less, whereas the mean duration of treatment in clinical practice is three to four months [98]. Reassuringly, time trends for suicide (England and Wales) [99] and non-fatal self harm (Oxford) [100] in children and adolescents provided no consistent evidence of adverse trends paralleling increased prescribing in the 1990s, although there was some evidence of a rise in non-fatal self harm in young females. Furthermore, in the United States, recent research suggests that areas with the largest increases in antidepressant prescribing to 10–19 year olds experienced the greatest falls in suicide [101]. Olfson et al. concluded that from the population perspective, the balance of risks and benefits of SSRIs is unclear. Any antidepressant-induced suicides may be offset by the beneficial effects of antidepressants on depression and long-term suicide risk associated with untreated depression. The low toxicity of SSRIs in overdose will have prevented some suicides. The balance of risks and benefits may vary depending on an individual's underlying suicide risk. For patients with conditions that have a high risk of suicide, such as severe depression [102], the risk-benefit balance may be more favourable than for patients with conditions such as anxiety and mild depression, in which suicide is rare. It is in these lower risk conditions, however, that much of the recent rise in prescribing has probably occurred [96].

The FDA Public Health Advisory published in October 2004 a statement on the risk of antidepressants to increased suicidality (suicidal thoughts and suicide attempts) in children or adolescents, based on the results of a joint meeting of the Psychopharmacologic Drug Advisory Committee and the Pediatric Drug Advisory Committee (September 2004). In this statement, the FDA put former statements with a one-sided focus on SSRIs into perspective and assigned the risk to all antidepressants. They also stated that there was no suicide in a huge dataset of 4,400 patients, but only suicide attempts. Based on these data, the FDA determined a boxed warning containing the key message that anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need [103].

In the statement of the Committee for Medicinal Products for Human Use (CHMP) in April 2005, the European Medicines Agency (EMEA) went in the same direction as the FDA but rather focused on the modern antidepressants. Beside the risk of suicidality, the statement also included the risk of hostility [104].

The FDA statement was based on an analysis published in 2006 [105].

Twenty-four placebo-controlled trials involving 4852 patients were included. Sixteen trials studied patients with major depressive disorder, 8 investigated other indications such as OCD or anxiety disorders. Only 20 trials were included in the risk ratio analysis because 4 trials had no event of this kind at all. A meta-analysis was conducted to obtain overall suicidality risk estimates for each drug individually, for selective serotonin reuptake inhibitors in depression trials as a group, and for all evaluable trials combined. There were no completed suicides in any of these trials. The overall risk ratio for selective serotonin reuptake inhibitors in depression trials was 1.66 (95% CI, 1.02–2.68) and for all drugs across all indications was 1.95 (95% CI, 1.28–2.98). The overall risk difference for all drugs across all indications was 0.02 (95% CI, 0.01–0.03).

The authors concluded that the use of antidepressant drugs in paediatric patients is associated with a modestly increased risk of suicidality. In the discussion the authors mention an interesting methodological problem: the lack of concordance in the signal for suicidality reported as an adverse event outcome and as ascertained with the suicide item in the depression rating scales. As a possible explanation for this discrepancy the authors propose the fact that the depression rating scales were administered at set times and may not have adequately captured suicidality events that occurred between scheduled visits. They note that the suicidality signal as determined by adverse event reporting was consistent whether focusing on suicidal ideation or behaviour.

The American College of Neuropsychopharmacology (ACNP) Task Force on SSRIs and Suicidal Behavior in Youth [106] refers primarily to the other publication by Hammad and comes to the same conclusion as the FDA.

Hammad et al. [105] also discuss the discrepancy between the results of this meta-analysis and the fact that the suicide rate in adolescents in the US has declined in recent years in association with the prescription rate of antidepressants. There are also ecological data suggesting that increasing prescriptions for antidepressant drugs in adolescents are associated with a decrease in adolescent suicide [101].

The licensing authorities may have particularly accentuated the risk in their statements since there is an unfavourable ratio between the allegedly recognised risk and the benefit, i.e., the efficacy. The better part of the SSRI studies in depressive children and adolescents (apart from the fluoxetine studies) was unable to show a statistically significant superiority of the antidepressant versus placebo with respect to antidepressive efficacy [107]. There is only positive evidence of efficacy in depression for fluoxetine [108]. However, the efficacy of treatment of obsessive compulsive disorder with SSRIs has been proven in children and adolescents [109]. It is regrettable that the statements do not contain a differentiated evaluation of the antidepressants with respect to their toxicity risk [110].

The statements of the regulatory authorities were criticised as leading to therapeutic abstinence [111]. Referring to this criticism, Hammad et al. [105]

pointed out that the FDA statement was not meant as a contraindication of antidepressants in paediatric use.

Summary

Negative effects of antidepressants on suicidality are difficult to investigate in empirical studies due to several methodological limitations. A broad scientific approach therefore has to use complementary methods to obtain the most comprehensive evidence.

Altogether, the empirical data seem to demonstrate a suicidality-decreasing effect of antidepressants [2]. Data from randomised controlled studies show a reduction of suicidal thoughts. Epidemiological data indicate an inverse relationship between antidepressant prescription rates and suicide rates: when the former increase the latter decrease.

As to the case reports on suicidality-inducing effects of antidepressants, one must be aware that these should be interpreted very cautiously and different kinds of bias and misperceptions inherent in case reports should be considered carefully. Case reports can be seen only as a source of hypotheses but not as confirmation of hypotheses. If only single case data are available, the extreme uncertainty of the evidence should be addressed and relevant conclusions should not be drawn.

Individual randomised, controlled studies do not supply much evidence to support the hypothesis that antidepressants in general or individual antidepressants have suicidality-inducing effects. Several meta-analyses comparing datasets of individual antidepressants, mostly SSRIs, demonstrated a greater average reduction of the suicidal thoughts score under SSRIs, as well as comparator drugs like TCAs, compared to placebo. In addition, the categories 'worsening of pre-existing suicidal thoughts' or 'new emergence of suicidal thoughts' were less frequent in the SSRI or TCA groups than in the placebo groups. Meta-analyses on datasets of novel antidepressants from national drug authorities which took the suicide attempt rate or suicide rate as the outcome criterion failed to demonstrate a suicidality-increasing effect of antidepressants. Only the meta-analysis by Fergusson et al. [53], which included the largest number of studies, found an increased risk of suicide attempts for SSRIs compared to placebo, but not different from TCAs.

A meta-analysis by the FDA of the antidepressant studies in children or adolescents found an increase of suicidal thoughts and suicide attempts but not suicide [103, 105]. This does not appear to be specific to the SSRIs, as the FDA correctly stated. However, such a potential risk for adults or children/adolescents is not mirrored by epidemiological data on the risk of suicide in the child/adolescent group.

Pharmacoepidemiological studies that investigated the association between the prescription risks for TCAs/SSRIs and suicide rates by applying sophisticated statistical methods showed no increased risk of suicide in association with antidepressants, especially no increase of suicide risk in conjunction with SSRIs. Four cross-sectional naturalistic studies on clinical samples and one naturalistic follow-up study failed to demonstrate a significant risk of SSRIs compared to TCAs in terms of suicidality, suicide attempts or suicide. Two naturalistic cross-sectional and one naturalistic follow-up study on clinical samples were not able to find differences between SSRIs and TCAs in terms of suicidality, suicide attempts or suicide. Some indications in this direction were no longer present after confounding factors were controlled for. Only two cross-sectional studies [20, 68] suggest that patients treated with SSRIs demonstrate a higher risk than patients treated with TCAs, when all methods of deliberate self-harm are counted together. However, it should be noted that the study by Donovan et al. [68] did not control for confounding factors, while the control of some confounding factors in the study by Didham et al. [20] reduced the increased risk substantially.

Related to this controversy of potential harmful effects of antidepressants in terms of suicidality is the issue of differences in the fatal toxicity of antidepressants. There is clear evidence that most modern antidepressants like the SSRIs have a lower fatal toxicity risk than the TCAs when a patient uses them to attempt suicide.

Even though statistical analyses of control group studies or pharmacoepidemiological/clinical data do not deliver consistent indications of a suicidality-inducing effect of SSRIs or antidepressants in adults in general, the principle possibility of such an adverse effect in single cases or in subgroups of patients should be considered carefully. Different mechanisms could principally lead to suicidality-enhancing effects. These might, for example, be related to the pharmacological mode of action related to different transmitter systems, to special pharmacodynamic properties like activating/drive-enhancing effects or side effects like akathisia. As to special dispositions of patients, personality disturbances such as borderline personality disorder, comorbidity, non-response, bipolarity and other factors should be considered [5, 32, 112, 113].

In the context of possible mechanisms for a potentially higher suicide rate, it deserves consideration that, as far as antidepressants are concerned, determination of the suicide risk of an individual patient or the general suicide rate is very complex and involves the integration of different factors. For example, the potential induction of suicidal thoughts or even suicidal ideation, of which the SSRIs are accused when compared to tricyclic antidepressants, may be compensated for by a much lower risk of a fatal outcome of a suicide attempt with an SSRI compared to a TCA. In the discussion about the po-

tential suicide-enhancing risks of the SSRIs it seems very problematic not to consider equally the much higher fatal toxicity indices of the TCAs.

It also seems to be of great importance that if there is a suicidality-inducing effect of SSRIs or antidepressants in general, this effect does not appear to translate into an increase in the risk of suicide: an increased prescription of antidepressants, preferentially SSRIs, generally leads to a reduction of suicide risk.

In everyday clinical practice the discussion about the possible risks of the SSRIs or antidepressants in general should not result in clinicians forgetting the benefits of these drugs, especially their lower fatal toxicity profile. This is a great advantage, especially in cases with severe suicidality. The choice of a less toxic antidepressant helps to avoid the risk of fatality if the patient should misuse the antidepressant for a suicide attempt.

Beside all these considerations, the symptoms of the acute depressive episode and the risk of relapse [114–116] require an effective drug treatment accompanied by the chance to reduce suicidal thoughts. The overcritical position, underestimating the efficacy of antidepressants in comparison to the risk of inducing suicidality [48, 117], should not be followed [118]. It should not be forgotten that psychosocial interventions, which are often suggested as an alternative, might be ineffective under certain circumstances [119] or can even induce suicidality [8, 9].

Of course, particularly at the start of treatment patients are often very labile and it is theoretically possible that in single cases antidepressants, probably depending on their specific pharmacological and pharmacodynamic characteristics and in interaction with special characteristics of the patient such as personality traits, comorbidity etc., can induce or enhance suicidal thoughts or even reduce the threshold level for suicide attempts. It is a question of good clinical practice to monitor every patient carefully, especially at the start of a drug treatment, and to try to avoid any kind of risk. In case of agitation, akathisia, sleep disturbances or other drug side effects that may potentially induce or enhance suicidality, a sedating or sleep-inducing comedication should be administered. It is also of greatest importance to offer the patient a substantial supportive psychotherapy. Finally, it should not be forgotten that depressive symptoms and suicidal thoughts can fluctuate during the day or over longer time periods. It is often difficult to follow this carefully enough on an outpatient basis, so that inpatient treatment might be a better option for patients at high risk.

References

1. Nemeroff CB, Compton MT, Berger J (2001) The depressed suicidal patient. Assessment and treatment. Ann N Y Acad Sci 932:1–23
2. Möller HJ (2006) Evidence for beneficial effects of antidepressants on suicidality in depressive patients: A systematic review. Eur Arch Psychiatry Clinl Neurosci 256:329–343
3. Milane MS, Suchard MA, Wong ML, Licinio J (2006) Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. PLoS Med 3:e190
4. Lapierre YD (2003) Suicidality with selective serotonin reuptake inhibitors: valid claim? J Psychiatry Neurosci 28:340–347
5. Möller HJ (1992) Antidepressants—do they decrease or increase suicidality? Pharmacopsychiatry 25:249–253
6. Baldwin D, Bullock T, Montgomery D, Montgomery S (1991) 5-HT reuptake inhibitors, tricyclic antidepressants and suicidal behaviour. Int Clin Psychopharmacol 6(Suppl 3):49–55
7. Isacsson G (2000) Suicide prevention—a medical breakthrough? Acta Psychiatry Scand 102:113–117
8. Möller HJ (1992) Attempted suicide: efficacy of different aftercare strategies. Int Clin Psychopharmacol 6(Suppl 6):58–69
9. Möller HJ (2003) Suicide, suicidality and suicide prevention in affective disorders. Acta Psychiatrica Scandinavica Supplementum:73–80
10. Walsh MT, Dinan TG (2001) Selective serotonin reuptake inhibitors and violence: a review of the available evidence. Acta Psychiatry Scand 104:84–91
11. Gunnell D, Middleton N, Whitley E, Dorling D, Frankel S (2003) Why are suicide rates rising in young men but falling in the elderly?—a time-series analysis of trends in England and Wales 1950–1998. Soc Sci Med 57:595–611
12. Mines D, Hill D, Yu H, Novelli L (2005) Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine, and citalopram. Pharmacoepidemiol Drug Saf 14:367–372
13. Rujescu D, Thalmeier A, Möller HJ, Bronisch T, Giegling I (2006) Molecular genetic findings in suicidal behavior: What is beyond the serotonergic system? Arch Suicide Res (in press)
14. Tollefson GD, Rampey AH Jr, Beasley CM Jr, Enas GG, Potvin JH (1994) Absence of a relationship between adverse events and suicidality during pharmacotherapy for depression. J Clin Psychopharmacol 14:163–169
15. Bauer MS, Wisniewski SR, Marangell LB, Chessick CA, Allen MH, Dennehy EB, Miklowitz DJ, Thase ME, Sachs GS (2006) Are antidepressants associated with new-onset suicidality in bipolar disorder? A prospective study of participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 67:48–55
16. Conner KR, Hesselbrock VM, Schuckit MA, Hirsch JK, Knox KL, Meldrum S, Bucholz KK, Kramer J, Kuperman S, Preuss U, et al. (2006) Precontemplated and impulsive suicide attempts among individuals with alcohol dependence. J Stud Alcohol 67:95–101
17. Fleischmann A, Bertolote JM, Belfer M, Beautrais A (2005) Completed suicide and psychiatric diagnoses in young people: a critical examination of the evidence. Am J Orthopsychiatry 75:676–683
18. Harris EC, Barraclough B (1997) Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry 170:205–228
19. Rihmer Z, Akiskal H (2006) Do antidepressants t(h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. J Affect Disord 94: 3–13
20. Didham RC, McConnell DW, Blair HJ, Reith DM (2005) Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. Br J Clin Pharmacol 60:519–525
21. Grimes DA, Schulz KF (2002) Bias and causal associations in observational research. Lancet 359:248–252
22. Warshaw MG, Keller MB (1996) The relationship between fluoxetine use and suicidal behavior in 654 subjects with anxiety disorders. J Clin Psychiatry 57:158–166
23. Teicher MH, Glod C, Cole JO (1990) Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 147:207–210

24. Dasgupta K (1990) Additional case of suicidal ideation associated with fluoxetine. Am J Psychiatry 147:1570
25. Hoover CE (1990) Additional case of suicidal ideation associated with fluoxetine. Am J Psychiatry 147:1570–1571
26. Masand P, Gupta S, Dewan M (1991) Suicidal ideation related to fluoxetine treatment. N Engl J Med 324:420
27. Rothschild AJ, Locke CA (1991) Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. J Clin Psychiatry 52:491–493
28. King RA, Riddle MA, Chappell PB, Hardin MT, Anderson GM, Lombroso P, Scahill L (1991) Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. J Am Acad Child Adolesc Psychiat 30:179–186
29. Vorstman J, Lahuis B, Buitelaar JK (2001) SSRIs associated with behavioral activation and suicidal ideation. J Am Acad Child Adolesc Psychiatry 40:1364–1365
30. Healy D (2000) Emergence of antidepressant induced suicidality. Primary Care Psychiatry 6:23–28
31. Healy D, Langmaak C, Savage M (1999) Suicide in the course of the treatment of depression. J Psychopharmacol 13:94–99
32. Möller HJ (2006) Pharmacological/clinical mechanisms by which antidepressants could theoretically induce suicidal ideations or behaviour. In preparation
33. Miller RA (1990) Discussion of fluoxetine and suicidal tendencies. Am J Psychiatry 147:1571–1572
34. Tollefson GD (1990) Fluoxetine and suicidal ideation. Am J Psychiatry 147:1691–1693
35. Teicher MH, Glod CA, Cole JO (1991) Fluoxetine and preoccupation with suicide – Dr Teicher and associates reply. Am J Psychiatry 148:1260–1262
36. Beasley CM Jr, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH Jr, Heiligenstein JH, Thompson VL, Murphy DJ, Masica DN (1991) Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. Br Med J 303:685–692
37. Hamilton M (1967) Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296
38. Montgomery SA, Dunner DL, Dunbar GC (1995) Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. Eur Neuropsychopharmacol 5:5–13
39. Aursnes I, Tvete IF, Gaasemyr J, Natvig B (2005) Suicide attempts in clinical trials with paroxetine randomised against placebo. BMC Med 3:14
40. Glaxo Smith Kline (2006) Paroxetine: Important safety information regarding the risk of suicidal behaviour. Letter to Healthcare Professionals (Europe). www.gsk.com/media/par_current_analysis
41. Pedersen AG (2005) Escitalopram and suicidality in adult depression and anxiety. Int Clin Psychopharmacol 20:139–143
42. Healy D, Whitaker C (2003) Antidepressants and suicide: risk-benefit conundrums. J Psychiatry Neurosci 28:331–337
43. Khan A, Warner HA, Brown WA (2000) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry 57:311–317
44. Khan A, Khan S, Kolts R, Brown WA (2003) Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 160:790–792
45. Brecher M (1991) FDA review and evaluation of clinical data original NDA 20–021, Paroxetine Safety Review June 19th
46. Lee H (1991) Statistical reviews on Sertraline for FDA, August 14th 1990 and January 31st 1991
47. Khan A, Khan SR, Leventhal RM, Brown WA (2001) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database. Int J Neuropsychopharmacol 4:113–118
48. Kirsch I, Moore TJ, Scoboria A, Nicholls SS (2002) The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. Prevention and Treatment. Article 23. Posted 15 Jul 2002. www.journals.apa.org/prevention/volume5/pre0050023a
49. Storosum JG, van Zwieten BJ, van den BW, Gersons BP, Broekmans AW (2001) Suicide risk in placebo-controlled studies of major depression. Am J Psychiat 158:1271–1275
50. Rouillon F (1994) Long-term care with antidepressants. Encephale 20:291–293
51. Rouillon F, Lejoyeux M, Filteau MJ (1992) Unwanted effects of long-term treatment. In: Rouillon F, Montgomery S (eds) Long-term treatment of depression. Perspectives in psychiatry. Chichester, John Wiley, pp 81–111
52. Gunnell D, Saperia J, Ashby D (2005) Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. Brit Med J 330:385
53. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B (2005) Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. Br Med J 330:396
54. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B (2005) Correction and clarification. BMJ 330:653
55. Holtmann M, Bolte S, Poustka F (2005) Suicidality in depressive children and adolescents during treatment with selective serotonin reuptake inhibitors Review and meta-analysis of the available randomised, placebo controlled trials. Nervenarzt Epub ahead of print
56. Carlsten A, Waern M, Ekedahl A, Ranstam J (2001) Antidepressant medication and suicide in Sweden. Pharmacoepidemiol Drug Saf 10:525–530
57. Gibbons RD, Hur K, Bhaumik DK, Mann JJ (2005) The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 62:165–172
58. Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ (2004) Antidepressants and suicide risk in the United States, 1985–1999. J Clin Psychiatry 65:1456–1462
59. Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P (2003) Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. Brit Med J 326:1008
60. Kelly CB, Ansari T, Rafferty T, Stevenson M (2003) Antidepressant prescribing and suicide rate in Northern Ireland. Eur Psychiatry 18:325–328
61. Rihmer Z (2001) Can better recognition and treatment of depression reduce suicide rates? A brief review. Eur Psychiatry 16:406–409
62. Fava M, Rosenbaum JF (1991) Suicidality and fluoxetine: is there a relationship? J Clin Psychiatry 52:108–111
63. Jick SS, Dean AD, Jick H (1995) Antidepressants and suicide. BMJ 310:215–218
64. Jick H, Kaye JA, Jick SS (2004) Antidepressants and the risk of suicidal behaviors. JAMA 292:338–343
65. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, Evans S, Gunnell D (2005) Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 330:389
66. Leon AC, Keller MB, Warshaw MG, Mueller TI, Solomon DA, Coryell W, Endicott J (1999) Prospective study of fluoxetine treatment and suicidal behavior in affectively ill subjects. Am J Psychiatry 156:195–201
67. Donovan S, Kelleher MJ, Lambourn J, Foster R (1999) The occurrence of suicide following the prescription of antidepressant drugs. Arch Suicide Res 5:181–192
68. Donovan S, Clayton A, Beeharry M, Jones S, Kirk C, Waters K, Gardner D, Faulding J, Madeley R (2000) Deliberate self-harm and antidepressant drugs. Investigation of a possible link. Br J Psychiatry 177:551–556
69. Henry JA, Alexander CA, Sener EK (1995) Relative mortality from overdose of antidepressants. BMJ 310:221–224
70. Simon GE, Savarino J, Operskalski B, Wang PS (2006) Suicide risk during antidepressant treatment. Am J Psychiatry 163:41–47

71. Mackay FJ, Dunn NR, Wilton LV, Pearce GL, Freemantle SN, Mann RD (1997) A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. Pharmacoepidemiol Drug Saf 6:235–246

71a. Tiihonen J, et al. (2006) Presentation S.13.03, 19th ECNP Congress, Paris, September 2006

72. Kerr GW, McGuffie AC, Wilkie S (2001) Tricyclic antidepressant overdose: a review. Emerg Med J 18:236–241

73. Whyte IM, Dawson AH, Buckley NA (2003) Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM 96:369–374

74. Gunnell D, Ho D, Murray V (2004) Medical management of deliberate drug overdose: a neglected area for suicide prevention? Emerg Med J 21:35–38

75. Freemantle N, House A, Song F, Mason JM, Sheldon TA (1994) Prescribing selective serotonin reuptake inhibitors as strategy for prevention of suicide. BMJ 309:249–253

76. Cassidy S, Henry J (1987) Fatal toxicity of antidepressant drugs in overdose. Br Med J (Clin Res Ed) 295:1021–1024

77. Farmer RD, Pinder RM (1989) Why do fatal overdose rates vary between antidepressants? Acta Psychiatr Scand Suppl 354:25–35

78. Henry JA (1989) A fatal toxicity index for antidepressant poisoning. Acta Psychiatr Scand Suppl 354:37–45

79. Ohberg A, Lonnqvist J, Sarna S, Vuori E, Penttila A (1995) Trends and availability of suicide methods in Finland. Proposals for restrictive measures. Br J Psychiatry 166:35–43

80. Henry JA (1997) Epidemiology and relative toxicity of antidepressant drugs in overdose. Drug Saf 16:374–390

81. Frey R, Schreinzer D, Stimpfl T, Vycudilik W, Berzlanovich A, Kasper S (2000) Suicide by antidepressant intoxication identified at autopsy in Vienna from 1991–1997: the favourable consequences of the increasing use of SSRIs. Eur Neuropsychopharmacol 10:133–142

82. Shah R, Uren Z, Baker A, Majeed A (2001) Deaths from antidepressants in England and Wales 1993–1997: analysis of a new national database. Psychol Med 31:1203–1210

83. Frey R, Schreinzer D, Stimpfl T, Vycudilik W, Berzlanovich A, Kasper S (2002) Fatal poisonings with antidepressive drugs and neuroleptics. Analysis of a correlation with prescriptions in Vienna 1991 to 1997. Nervenarzt 73:629–636

84. Cheeta S, Schifano F, Oyefeso A, Webb L, Ghodse AH (2004) Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. Br J Psychiatry 184:41–47

85. Ghodse H, Oyefeso A, Webb L, Pollard M, Shifano F, Corkery J (2002) Drug-related deaths as reported by coroners in England and Wales, January-June 2001 (np-SAD Surveillance Report no. 8). St George's Hospital Medical School, London

86. Kapur S, Mieczkowski T, Mann JJ (1992) Antidepressant medications and the relative risk of suicide attempt and suicide. JAMA 268:3441–3445

87. Isacsson G, Holmgren P, Ahlner J (2005) Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. Acta Psychiatr Scand 111:286–290

88. Bateman DN, Chick J, Good AM, Kelly CA, Masterton G (2004) Are selective serotonin re-uptake inhibitors associated with an increased risk of self-harm by antidepressant overdose? Eur J Clin Pharmacol 60:221–224

89. Möller HJ (2004) SSRIs: are the accusations justified? World J Biol Psychiatry 5:174–175

90. Andrade C, Bhakta SG, Singh NM (2006) Controversy revisited: Selective serotonin reuptake inhibitors in pediatric depression. World J Biol Psychiatry 7:251–260

91. Hjalmarsson L, Corcos M, Jeammet P (2005) Selective serotonin reuptake inhibitors in major depressive disorder in children and adolescents (ratio of benefits/risks). Encephale 31:309–316

92. Scahill L, Hamrin V, Pachler ME (2005) The use of selective serotonin reuptake inhibitors in children and adolescents with major depression. J Child Adolesc Psychiatr Nurs 18:86–89

93. Wohlfarth TD, van Zwieten BJ, Lekkerkerker FJ, Gispen-de Wied CC, Ruis JR, Elferink AJ, Storosum JG (2006) Antidepressants use in children and adolescents and the risk of suicide. Eur Neuropsychopharmacol 16:79–83

94. Wong IC, Besag FM, Santosh PJ, Murray ML (2004) Use of selective serotonin reuptake inhibitors in children and adolescents. Drug Saf 27:991–1000

95. Vitiello B, Swedo S (2004) Antidepressant medications in children. N Engl J Med 350:1489–1491

96. Gunnell D, Ashby D (2004) Antidepressants and suicide: what is the balance of benefit and harm. BMJ 329:34–38

97. Nutt DJ (2003) Death and dependence: current controversies over the selective serotonin reuptake inhibitors. J Psychopharmacol 17:355–364

98. Mackay FR, Dunn NR, Martin RM, Pearce GL, Freemantle SN, Mann RD (1999) Newer antidepressants: a comparison of tolerability in general practice. Br J Gen Pract 49:892–896

99. McClure GM (2001) Suicide in children and adolescents in England and Wales 1970–1998. Br J Psychiatry 178:469–474

100. Hawton K, Hall S, Simkin S, Bale L, Bond A, Codd S, Stewart A (2003) Deliberate self-harm in adolescents: a study of characteristics and trends in Oxford, 1990–2000. J Child Psychol Psychiatry 44:1191–1198

101. Olfson M, Shaffer D, Marcus SC, Greenberg T (2003) Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 60:978–982

102. Harris EC, Barraclough B (1998) Excess mortality of mental disorder. Br J Psychiatry 173:11–53

103. FDA Public Health Advisory (2004) Suicidality in children and adolescents being treated with antidepressant medications. www. fda.gov/cder/drug/ antidepressants/SSRIPHA200410

104. Emea (2005) European Medicines Agency finalises review of antidepressants in children and adolescents. www. emea. eu.int/pdfs/human/press/ pr/12891805en

105. Hammad TA, Laughren T, Racoosin J (2006) Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 63:332–339

106. Mann JJ, Emslie G, Baldessarini RJ, Beardslee W, Fawcett JA, Goodwin FK, Leon AC, Meltzer HY, Ryan ND, Shaffer D et al (2006) ACNP Task Force report on SSRIs and suicidal behavior in youth. Neuropsychopharmacol 31:473–492

107. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL (2004) Efficacy and safety of antidepressants for children and adolescents. BMJ 328:879–883

108. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E (2004) Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 363:1341–1345

109. Geller DA, Biederman J, Stewart SE, Mullin B, Martin A, Spencer T, Faraone SV (2003) Which SSRI? A meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder. Am J Psychiatry 160:1919–1928

110. Nutt DJ (2005) Death by tricyclic: the real antidepressant scandal? J Psychopharmacol 19:123–124

111. Brent DA (2004) Antidepressants and pediatric depression—the risk of doing nothing. N Engl J Med 351:1598–1601

112. Balazs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS (2006) The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. J Affect Disord 91:133–138

113. Teicher MH, Glod CA, Cole JO (1993) Antidepressant drugs and the emergence of suicidal tendencies. Drug Safety 8:186–212

114. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM (2003) Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 361:653–661

115. Reynolds CF III, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters MA, Stack JA, et al. (2006) Maintenance treatment of major depression in old age. N Engl J Med 354:1130–1138
116. Volz HP, Baghai TC, Möller HJ (2006) Drug treatment of depression in the 2000s—an overview of achievements in the last ten years and future possibilities. World J Biol Psychiatry 7:198–222
117. Moncrieff J, Kirsch I (2005) Efficacy of antidepressants in adults. BMJ 331:155–157
118. Geddes JR, Cipriani A (2004) Selective serotonin reuptake inhibitors. BMJ 329:809–810
119. Vaiva G, Vaiva G, Ducrocq F, Meyer P, Mathieu D, Philippe A, Libersa C, Goudemand M (2006) Effect of telephone contact on further suicide attempts in patients discharged from an emergency department: randomised controlled study. BMJ 332:1241–1245