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Do SSRIs or antidepressants in general increase suicidality?

WPA Section on Pharmacopsychiatry: consensus statement

■ **Abstract** In the past few years several papers have reported critically on the risk of suicidal thoughts and behaviour associated with antidepressants, primarily SSRIs. The risk-benefit ratio of antidepressant (AD) treatment has been questioned especially in children and adolescents. The critical publications led to warnings being issued by regulatory authorities such as the FDA, MHRA and EMEA and stimulated new research activity in this field. However, potential harmful effects of antidepressants on suicidality are difficult to investigate in empirical studies because these have several methodological limitations. Randomised controlled trials (RCTs) are the most reliable way to test the hypothesis that AD have such side effects. In addition to meta-analyses of RCTs, complementary research methods should be applied to obtain the most comprehensive information. We undertook a comprehensive review of publications related to the topics ADs, suicide, suicidality, suicidal behaviour and aggression. Based on this comprehensive review we conclude that ADs, including SSRIs, carry a small risk of inducing suicidal thoughts and suicide attempts, in age groups below 25 years, the risk reducing further at the age of about 30–40 years. This risk has to be balanced against the well-known beneficial effects of ADs on depressive and other symptoms (anxiety, panic, obsessive-compulsive symptoms), including suicidality and suicidal behaviour. According to the principles of good clinical practice, decision making should consider carefully the beneficial effects of AD treatment as well as potentially harmful effects and attempt to keep the potential risks of AD treatment to a minimum. It is the major problem facing efforts to identify the possible 'suicidal effects' of antidepressants.

■ **Key words** antidepressants · suicidality · suicidal behaviour · suicide

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Introduction

A wave of uncertainty about the possible risks for suicidality of antidepressant (AD) treatment has flowed through child and adolescent psychiatry, and from there has spread into adult psychiatry. It was initiated by information and warnings from regulatory authorities such as the American Food and Drug Administration (FDA) [20, 21], the British Medicines and Healthcare Products Regulatory Agency (MHRA) [86], and the European Medicines Evaluation Agency (EMEA, CHMP) [16] claiming that induction of suicidality should be seen as a serious side effect of the selective serotonin reuptake inhibitors (SSRIs) and some other ADs in children and adolescents, and that the use of ADs in these groups should be highly restricted [77]. Although the concerns primarily focussed on the SSRIs, they later spread to include the tricyclic antidepressants (TCAs). On the basis of several reanalyses not only children and adolescents but also younger adult patients were seen to be an at-risk group.

The problem has been presented as a shocking new finding, but it is not as new as many people seem to believe. For decades it has been part of medical

teaching that treatment can have an early stimulating effect such that depressed patients may acquire the energy to follow through on suicidal impulses before the mood improvement associated with AD or other treatment takes effect. This so-called drive-mood dissociation in the early phase of AD treatment has long been seen as a special risk factor for suicidal behaviour (see e.g. [84]), and physicians were warned to observe patients carefully in this phase and to deal pragmatically with the potential risks: this has formed a principle of good clinical practice. Therefore early in treatment, frequent visits and supportive psychotherapy are recommended, and a preference for sedative ADs and/or co-medication with benzodiazepines was also thought to reduce the risk of suicidal behaviour. However, these suggestions are based on clinical experience and there has been little evidence to support them.

The classical drive-mood dissociation was thought of as a property of the course of illness, not as a side effect of any given treatment. However, the idea that SSRIs in particular can provoke agitation and associated suicidal thoughts is also not new. Indeed, the recent surge of interest is redolent of something that occurred more than a decade ago, shortly after the introduction of the first widely used SSRI, fluoxetine, to adult psychiatric practice. At that time the discussion was initiated by the description of a case series in which suicidal thoughts had arisen apparently de novo during treatment with fluoxetine [122]. Further case reports followed, including child and adolescent cases of increased impulsivity after SSRIs. These findings were far from conclusive: for example, most of the patients were being treated with several drugs simultaneously. But, as is sometimes the case with anecdotal observations, important questions were raised—namely whether SSRIs might provoke suicidality and possibly other types of autoaggressive or even heteroaggressive behaviours; whether this is specific to SSRIs or a risk of all ADs; if other psychotropic drugs such as benzodiazepine share this risk [91]. As with any anecdotal observations, they posed the more substantial question: is there a confirmatory signal in larger collections of more representative data? Accordingly, efforts were made to give quantitative answers to the questions. Pooled analyses of data from placebo-controlled clinical studies available from pharmaceutical companies, e.g. for fluoxetine and paroxetine, were unable to confirm in the early stage of this controversy the hypothesis that SSRI treatment might induce suicidality or suicide [6, 73, 80, 100, 121]. Other reviews even suggested that emergent suicidal ideation was lessened by SSRIs [3, 128]. In any case, because these drugs were so obviously an advance over TCAs in regard to safety in overdose, and in the majority of cases tolerability, most psychiatrists were prepared to accept the possibility that SSRIs had occasional adverse effects like agitation, even if such effects intensified subjective distress.

For perhaps 10 years, psychiatrists and primary care doctors continued to use SSRIs in adults because they were convinced of their efficacy and were happy with their safety. However, the hypothesis that SSRIs may induce suicidal thoughts, attempted or completed suicide and even homicide re-acquired active support [49] and even formed the basis for legal judgement against at least one pharmaceutical company [7, 32].

This development followed intensive marketing efforts which saw widening of SSRI use to a less severely ill population of depressed patients in primary care and, largely by extrapolation because the efficacy data were either absent or less convincing, to depressed children. It is this broader use that seems to have changed the balance of the argument between risk and benefit. The current controversy, starting with children and adolescents, has resulted in a renewed debate about SSRI-induced suicidality in adults [95]. The FDA put tight restrictions on the use of SSRIs and other ADs in children and adolescents [20]. CHMP followed but focussed on newer ADs [16]. Do we have to expect a similar development for the use of SSRIs in adults [99]? Is there solid evidence that SSRIs carry a higher risk of inducing/aggravating suicidality compared to other ADs, especially TCAs? Is the risk balanced against the beneficial consequences of treatment with ADs according to the principles of good clinical practice?

This document tries to answer these questions. The basis for this comprehensive review was a MEDLINE search from the year 1990 to 2007 for publications related to the topics ADs, suicide, suicidality, suicidal behaviour and aggression. Manual searches of pertinent journal article references and of the websites of the Food and Drug Administration and the European Medicines Agency were also performed. The results of this systematic review were first published in two papers, one on the positive and one on the negative affects of ADs concerning suicidality [96, 97]. For this current review, papers have been included that were published in 2006 and the first half of 2007 and were therefore not considered in the above mentioned reviews; the FDA clinical review on the relationship between antidepressant drugs and suicidality in adults [120] and the memorandum concerning the FDA hearing in December 2006 [74] are also of particular relevance.

Methodological problems associated with the analysis of effects of antidepressants on suicidality

When considering studies performed to analyse the effects of ADs on suicidality, one should differentiate between several phenomena: suicidal thoughts, suicide attempts and (completed) suicides [94]. The literature on suicidology, including publications on

predictor research, underline the fact that these phenomena can only represent to a limited degree a single basic concept—suicidality—even though they may appear sequentially in the rare patient who commits suicide. The risk factors for the individual phenomena are not wholly consistent [71, 72, 75, 90]. For example, simple sociodemographic data such as age and sex are of different relevance for suicide attempts and suicides: women and younger people have a greater risk of attempted suicide, whereas men and older people are more likely to commit suicide [94]. There are also findings indicating that ADs might have a different, even opposing influence on different phenomena of suicidality [96, 97]. For example, the risk for suicide attempts might increase while the risk for completed suicide might decrease.

Given this background, it does not appear meaningful to assess suicidal phenomena as an outcome, by using a quasi ordinal scale which ranks suicide at the upper, suicidal thoughts at the lower end, with suicide attempts in between [68]. Such a dimensional metric, originally suggested by the 'Columbia group' [107], was applied as a coding system for the preparation of the FDA review of the relationship between psychotropic drugs and suicidality in children and adolescents [39]. A similar 'ranking according to specificity for risk of suicide' was used in the recent FDA meta-analysis of the effects of ADs on suicidality in adults [74, 120]. Although these phenomena must be partially linked, it could be misleading to present them in a unidimensional hierarchy. Since they are associated with different risk factors, and potentially have different phenomenological bases, every suicide attempt is not a 'failed' suicide but often an independent event, a 'parasuicidal act' [23] with different motivations and intentions. These often lie outside the realm of autoaggression or life-threatening behaviour and may include, for example, the wish for temporary oblivion or to demonstrate desperation/frustration to a partner. Much more attention should be paid to the concept of parasuicide as an entity distinct from suicide [69] in order to achieve a better understanding of the phenomenological complexity which stops well short of a simple intention to die.

The system used in the FDA meta-analysis to code possible suicidal effects of ADs in adults specified three categories besides completed suicide, suicide attempt, preparatory acts toward imminent suicidal behaviour and suicidal ideation: these are 'self-injurious behaviour, intent unknown', 'Not enough information (fatal)' and 'Not enough information (non-fatal)' [120]. Whilst it makes sense clinically to include 'self-injurious behaviour intent unknown', it is often extremely difficult to determine the suicidal intention or non-suicidal intention of a self-destructive event because patients often either try to hide suicidal intention or they are not aware of it themselves. In order to overcome these problems of differential diagnosis and to cover the full spectrum of

different motivations/intentions of self-destructive acts (traditionally referred to as 'suicidal attempts'), the suicidologist Kreitman [69, 70] suggested that the criterion of suicidal intention be omitted and that the term 'parasuicide' be used instead of suicide attempts. Whether or not this rigorous approach, which of course also has its own limitations, is followed, it should at least be considered that omission of the criterion 'suicidal intention' results in suicide attempts in the traditional sense being underestimated, which might be a special problem in the clinical trial setting where doctors might have a tendency not to diagnose a suicide attempt. Thus when evaluating AD-related suicidal behaviour it seems correct to include the category 'self-injurious behaviour intent unknown' in addition to the traditional category 'suicide attempt'.

The importance of the definition of suicidality used in studies of possible causal associations with AD treatment is also relevant when considering the results of the meta-analysis by Fergusson et al. about the risk of suicidality in the context of treatment with SSRIs [22]. In contrast to traditional terminology, the authors defined 'suicide attempts' as including 'both fatal and non-fatal acts of suicide', and used this category as the primary outcome criterion. In the discussion of their finding of an increased rate of 'suicide attempts' (defined according to their unusual terminology) with SSRIs compared to placebo, Fergusson et al. [22] underline that the relative increase of 'suicide attempts' during SSRI treatment was restricted to 'non-fatal suicide attempts', and did not include 'fatal suicide attempts'—which is a most important differentiation.

Thus, when analysing the effects of AD on suicidality the differentiation between at least some of the different phenomena of suicidality, e.g. suicidal ideation, suicide attempt, suicide, should be considered. Furthermore, attempts should be made to disentangle drug effects on suicidality itself from effects on drive, autoaggression and impulsive behaviour, which can themselves influence suicidal behaviour [92, 123]. Finally, major predictors/risk factors for suicidality should be taken into account.

The results of randomised controlled trials, especially when placebo controlled, would seem to be the best basis for making statements about the suicide risk of ADs. However, there is only a low rate of suicidal behaviour in these studies, partly due to selection against patients with expressed risk intent. Suicidal ideation is somewhat more frequent and therefore differences between two treatment groups are more likely to become apparent. Generally, the results of such control group studies have to be evaluated critically under consideration of the methodological pitfalls inherent in the design of such trials. For example, most studies do not include patients with high suicidality and therefore do not provide data for the most relevant risk groups. The opposite is

true: 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 III studies. These comorbidity conditions can increase the risk of suicidality itself, either directly through increased impulsivity or via paradoxical drug effects. The exclusion of suicidal patients and patients with special risks lowers the basal rate of suicidal phenomena, and this reduces the likelihood of detecting a difference in suicidal phenomena between the experimental groups. Furthermore, study doctors pay careful attention to the early recognition of suicidal crises and intervene early in such cases, e.g. with additional medication or psychotherapeutic approaches, which also significantly reduces the chance to delineate a drug effect on suicidal behaviour. It should also be considered that any drug effects on suicidal behaviour might be of such a small size that they do not reach statistical significance in a trial powered, like all phase III studies, for the primary efficacy criterion of an AD trial, i.e. the reduction of depressive symptoms and not for detecting differences in suicidal ideation or suicidal behaviour.

There is another aspect which may confound the results: 'overdose' might sometimes not be detected as such in the placebo group because it has no medical consequences. This may result in an apparently lower rate of suicidal behaviour in the placebo group, at least as far as cases are concerned in which the medication in the respective trial arm is used as the method of deliberate self-harm.

Without going into all the details of potential methodological pitfalls, another point brought up by Stone and Jones [120] should be mentioned. If the propensity to suicide is associated with intolerance of drug side effects, subjects who eventually harm themselves may leave the study before experiencing the event if they are assigned to drug, but stay in the trial if they are assigned to placebo. Conversely, placebo subjects may drop out of a study due to a lack of relief from symptoms other than suicidality and later have a suicidality event, but subjects assigned to ADs may experience sufficient relief of other depressive symptoms to remain in the trial until a suicidality event occurs. This type of problem is difficult to verify because little information about subjects is consistently and reliably available after they leave a study.

In the earlier stages of research in this field only drug trials in depressed patients were considered. Later on, drug trials in other indications including anxiety disorders and OCD were also considered, especially in some meta-analyses. Because the potential risk of AD might differ in these different disorders (see for example [22]), it seems necessary to perform meta-analyses focussing on differing disorders, in addition to the meta-analyses of the whole data bases.

Because the difficulties mentioned above make it difficult to clarify the question of effects of AD on suicidality in controlled clinical studies, pooled analyses/meta-analyses were performed to improve the chance of finding information about different effects on suicidality phenomena between ADs and placebo or between different groups of ADs. Particularly in placebo-controlled studies, the study designer and/or the study physicians have a strong incentive to exclude suicidal patients right from the start or as soon as the patient's condition worsens during the study, which may result in a lower rate of suicidal behaviour in placebo-controlled trials. Such a lowering of the risk for suicidal behaviour may not be present to such a degree in active comparator studies. If meta-analyses pool results from placebo-controlled and active comparator studies, the higher risk of suicidal behaviour in the latter could result in SSRIs and/or TCAs appearing to have a higher risk than placebo. To avoid this bias, conclusions should be based only on placebo-controlled studies, or this effect should at least be controlled in pooled analyses that mix both types of studies.

Additional methods of obtaining evidence are required in order to obtain at least a complementary view; these include different kinds of epidemiological analyses, naturalistic follow-up studies, evaluation of complex interventions and also clinical experience with single cases. However, the specific limitations of each of these approaches have to be carefully considered.

Pharmacoepidemiological studies collect aggregate and not individual data, for example, national suicide rates are compared with national AD prescription rates, etc. It is of great importance that these data are analysed by multivariate statistical procedures taking into account as many as the most relevant confounders (like type of AD, gender, age, unemployment rate, alcohol consumption) as possible in the calculation. Such studies are also limited to the extent that they can normally only analyse data on suicides but not on suicide attempts.

Clinical cohort studies try to overcome these shortcomings 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 ADs. Unfortunately, the risk differences found in these studies are often not controlled for potential confounding factors that may critically influence the findings and therefore generate misleading results. One such confounding factor is selection bias in prescribing attitudes, e.g. patients judged as having a higher risk for suicidality are likely to be prescribed SSRIs which are known to have a lower fatal toxicity index. 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. But it is well known that elderly

patients have a higher risk for suicide. It is difficult to control all the possible confounding factors, especially if only data from one naturalistic sample are available and 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 all individuals with a critical event are really captured from the whole population of treated patients, or whether only a certain (selected) proportion are detected post hoc, while others do not show up in the database. Nevertheless, case control studies represent a meaningful approach if not too much significance is placed on the results in isolation. Of especial interest are huge detailed datasets on individual patients that are available from different routine care settings. In such a case-control study, the cohort of cases showing the unwanted events under certain treatment conditions may be compared 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 risk of significant bias remains. For example, in most of these studies differentiated information on psychopathological items such as standardised rating of depression symptoms is 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.

In studies investigating the risk of increased suicidality under treatment with ADs much more attention should be paid to general risk factors [36, 89, 116, 126], as well as diagnosis and comorbidity [5, 13, 24, 42, 111]. Consideration of such confounding factors in the statistical analysis can have significant effects on the risk analysis results, as was shown in several cohort studies [15]. Unfortunately, in most studies only easily accessible risk factors are considered, while others which require more sophisticated clinical investigation are often neglected. Principally, these investigations should go beyond the question whether there is a slightly increased risk of suicidality in the whole population treated with ADs and should focus much more on the question whether there is a pronounced risk in certain clinical subgroups.

Even if all relevant confounding factors are taken into account, observational studies are still unable to replace experimental studies because of their lack of specific validity. The general limitations of observational studies become apparent primarily in studies determining an association between a treatment and an outcome when the outcome itself is strongly associated with the condition being treated. For example, an observational study on 654 anxiety disorder patients [132] found that patients with more suicide risk factors at intake were more likely to be treated with fluoxetine than those without these risk factors. This is called confounding by indication, and it may lead to erroneous conclusions that a treatment results in an adverse outcome [33]. It is the major problem facing efforts to identify the possible 'suicidal effects' of antidepressants.

Single case reports are often seen to be an important way to detect suicidality-inducing effects of ADs. However, it is important to recognize the possibly inflated impact of single case results. For example, single case reports 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 large data sets (e.g. epidemiological case control studies). Causal interpretation based on individual case reports or personal accounts is extremely prone to false perceptions and bias. Because only a limited amount of theoretical knowledge is available, 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 AD and an increase of suicidality. However, a series of restrictions then have to be imposed in order to put the conclusions into perspective and to avoid one-sided interpretation [97].

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

The available evidence that ADs can induce or exacerbate suicidal tendencies originates from case reports mainly. Several of these were published after the advent of the SSRIs. In the early 1990s, the discussion whether a particular group of ADs might have a certain risk of increasing suicidal ideations/behaviour [91] was stimulated by the case series reported by Teicher et al. [122], 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 with time. The authors hypothesised that this might represent a risk of treatment with fluoxetine, an entirely defensible hypothesis to explain what they had seen. The paper by Teicher et al. induced others to report similar fluoxetine cases, mostly in single patients [14, 46, 54, 83, 112]. King et al. [66] reported a case series of adolescent patients who developed thoughts of self-harm or self-harming behaviour during treatment

with fluoxetine. Other case reports suggested that other SSRIs had the same effects, especially paroxetine in children and adolescents [66, 131]. These case reports did not confirm the hypothesis, but simply reinforced the need to try and exclude or accept it on the basis of more controlled data.

During treatment with ADs or other psychoactive drugs not only suicidality but also aggressiveness and other paradoxical effects have been reported as case reports [49, 91]. Some authors suggested that akathisia (induced by SSRIs) might trigger the induction or worsening of suicidality [4, 45, 48, 112]. Certain subgroups of patients, such as those with borderline personality disorders, seem to be especially vulnerable to such paradoxical effects [98]. However, other personality traits or personality disorders may also dispose to such paradoxical reactions. There are also some indications that patients with milder depression have a higher risk of reacting with increased suicidality or paradoxical reactions than the most severely depressed.

The methodology of case reports in this field, especially that of Teicher et al. [122], was criticised [88, 125] and objections raised to the hypothesised causal relationship, given the complex clinical situation, which sometimes included co-medication and other predisposing factors. The critical statements made by Miller [88] and Tollefson [125] about the early case series [122] give an impression of the methodological problems. Thus, these case reports require critical consideration, also in light of the methodological problems discussed above.

Results of pooled analysis of drug company databases

In general, no significant indication of increased suicidality has been obtained from individual SSRI studies [96], which is largely attributable to small sample size. For this reason, pooled analyses/meta-analyses were performed to try to minimise the risk of missing important effects.

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 TCA ($n = 731$) or placebo ($n = 569$), or both, was performed by Beasley et al. [6]. 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 [6]. Indeed, the opposite was true, as fluoxetine was significantly superior to placebo ($P < 0.001$) in reducing 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 [100]. The mean scores of the suicide item on the HAMD (a composite of suicidal thoughts and acts) showed 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 ($P < 0.05$). The comparator drugs had a similar advantage over placebo ($P < 0.05$). The same paper [100] also included an analysis of the data from the group of controlled studies mentioned above, together with data from extensions of controlled studies and open studies. 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 [100].

In response to a request by the FDA for data from AD manufacturers for an analysis of adult suicidality in 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 depressive and non-depressive disorders (e.g., dysthymia, panic disorder, generalized anxiety disorder and obsessive compulsive disorder). These trials included 8958 patients treated with paroxetine and 5953 with placebo [32]. The results showed a higher frequency of suicidal behaviour in young adults (prospectively defined as age 18–24 years) treated with paroxetine compared with placebo [17/776 (2.19%) vs. 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 disorders. In the older age groups (25–64 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%) vs. 1/1978 (0.05%)]. This difference was statistically significant; however, as the absolute number and incidence of events was unexpectedly small in the placebo group, GSK recommended 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 might extend beyond the age of 24 years. 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.

A pooled analysis of 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 [106] found 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 < 0.001, respectively). In the analysis of the proportion 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).

Altogether, the above mentioned pooled analyses of drug companies' data sets on their respective SSRIs failed to demonstrate a statistically significant increased risk for suicidal behaviour compared to either placebo or standard comparator drugs. The same is true for the risk of emergent/increasing suicidal ideation. However, the recent analysis of the paroxetine database demonstrated a small increase of suicide attempts. The mean scores of suicidal ideation declined during treatment with SSRIs in all pooled analyses in which this prospective criterion was analysed. Although these analyses appear to have been performed carefully using sophisticated analytical methods, some methodological issues exist that might have influenced the results. Furthermore, analyses showing increased suicidality or other negative effects of drugs may not always be published.

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

Considering the low basal risk of suicidal attempts and especially of completed suicide, one can argue that drug company databases for one individual AD might be biased or are still too small to have sufficient statistical power to give an indication of its individual effects. Following this line of argument, meta-analyses based on the large data sets available to drug authorities might represent a better approach to test the hypothesis of an increased suicide risk associated with SSRIs or ADs in general.

Khan et al. [64] assessed suicides, suicide attempts and depressive symptom reduction in the dossiers of 7 new ADs available in the FDA database. A large proportion of the investigational ADs were SSRIs or SNRIs (venlafaxine), but nefazodone, mirtazapine and bupropion were also included. Imipramine or amitriptyline were mostly used as the active comparator. Most data were from depression studies, but some were from preliminary studies in OCD or panic disorder. 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 ADs, 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 ($n = 2{,}805$).

In the context of the FDA summary reports, a larger sample of controlled clinical trials (the dossiers for nine modern FDA-approved ADs, including venlafaxine and citalopram) was analysed for differences in the suicide rate of SSRIs, standard comparators (mostly TCAs but also mianserin, mirtazapine, nefazodone, trazodone and maprotiline) and placebo [64]. 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 ADs (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 AD- and placebo-treated depressed subjects in controlled trials, or a difference between SSRIs and either other types of ADs or placebo [65].

The pooled analysis performed by Storosum et al. [121] was based on the registration dossiers of AD 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 [121].

The suicide rates found in the meta-analysis by Storosum et al. [121] seem to be marginally lower than those found by Khan et al. [64]. 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 maintenance treatment or long-term studies are often not published or that little respective information is given, as was also pointed out by Strorosum et al. [121], so that the data that are published are quite selective. Nevertheless, they probably focus on the time of highest risk, when depression ratings are high.

In the context of their pooled analysis of registration dossiers described above, Storosum et al. [121] identified by a Medline search all long-term, placebo-controlled AD studies conducted in the previous 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 these long-term studies it should be considered that the basal rate of suicide attempts was low, i.e. up to 0.2%, even under long-term conditions (the duration of most of the studies was one year). A similar result was found in an earlier meta-analysis of long-term trial data by Rouillon [113, 114], although this analysis found slight numerical differences favouring the placebo group.

The meta-analysis of SSRI studies in adult patients performed by Gunnell et al. [37] was based on a huge database submitted to the UK regulatory authority which 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. The data on suicidal thoughts are from documentation of side-effects and not based on rating scales. The authors found no evidence that SSRIs increased the risk of suicide. There was weak but not statistically significant evidence of an increased risk of self-harm (odds ratio 1.57, confidence interval 0.99–2.55). Risk estimates for suicidal thoughts were compatible with a modest not statistically significant protective effect (0.77, 0.37–1.55). As in most meta-analyses, the authors had no access to trial or patient level data and so could not conduct certain analyses, e.g. stratification by age.

The meta-analysis by Fergusson et al. [22] was based on a Medline search and on the Cochrane Collaborations register (November 2004), produced by the Cochrane depression, anxiety and neurosis meta-analytical groups, and included 945 randomized controlled group studies. 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. The active non-SSRIs were divided into a group of TCAs and a group with therapeutic interventions other than TCAs– including moclobemide, maprotiline, mianserin and psychotherapy, which is quite an unusual cluster. Seven hundred and two trials with 87,650 patients were initially reviewed, 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. Thus, this sample of trials overlapped with but differed from the other meta-analyses described above.

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 1.14–4.55, number needed 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 overall difference remained (2.70, 1.22–5.97; $P = 0.001$). In the comparison of 'fatal suicide attempts', no difference was detected between SSRIs and placebo (0.95, 0.24–3.78). In the pooled analysis of SSRIs versus TCAs, no difference in the odds ratio of 'suicide attempts' (0.88, 0.54–1.42) was detected. The odds ratio of 'non-fatal suicide attempts' for SSRIs compared with TCAs was 0.85 (0.51–1.43) and the odds ratio of 'fatal suicide attempts' was 1.08 (0.28 to 4.09). 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. However, this is still a weak effect given the calculated number needed to harm of 684. It is also not possible to understand how the difference in trial sample led to a slightly different result from, for example, the Gunnell study.

In a recently published meta-analysis, Hammad et al. evaluated the rate of suicide in placebo- and active drug-treated groups of patients with major depressive disorder (MDD) and various anxiety disorders participating in short-term randomized controlled trials (RCTs) [41]. The authors examined data from all manufacturer-sponsored short-term RCTs of nine commonly used ADs (four atypical ADs: buproprion, nefazodone, mirtazapine, venlafaxine; five SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline; and three TCAs: desipramine, amitriptyline, imipramine) in patients with MDD. Data were available for 207 trials conducted in patients with MDD, including a total of 40,028 patients; there were 21 cases of suicide in these patients.

The authors stratified data by type of trial (placebo-controlled vs. active-only controlled) and location of trial (North American vs. non-North America). The stratification according to location was considered important because suicides were far more common in trials performed outside North America: of the 16 suicides in MDD trials with only an active control comparison group, 14 were observed in the non-North American trials (according to the authors this imbalance may have been related to the fact that the non-North American trials included a relatively higher proportion of inpatients). Furthermore, as placebo-controlled trials were not usually conducted outside North America, a disproportionate amount of the placebo person-time came from North America, where fewer suicides occurred. The authors calculated rates of suicide per 100,000 person-years and compared them using rate ratios. They found a nearly 10-fold higher incidence of suicide in active-only controlled trials compared with placebo-controlled trials (11.1/1000 vs. 1.5/1000 person-years, respectively). The hypothesis that this might have reflected more severe depression upon entry into the study (i.e. a patient who is more sick may be more likely to be enrolled in an active-only controlled study to ensure he receives active treatment), was not reflected in the mean HAMD-17 severity scores at baseline. In the placebo-controlled MDD trials, the rate ratios of suicide in the combined drug groups compared with placebo were 1.1 (CI, 0.1–63.4) and 0.5 (CI, 0.0–36.7) for the non-North American and North American trials, respectively. In the non-North American strata of active-only controlled trials, the rate ratios of suicide (compared with TCAs as the reference group) were 1.0 (CI, 0.2–6.1) for the SSRIs and 1.5 (CI, 0.3–9.5) for the atypical ADs. These results suggest that suicide risk does not differ across the various treatment groups.
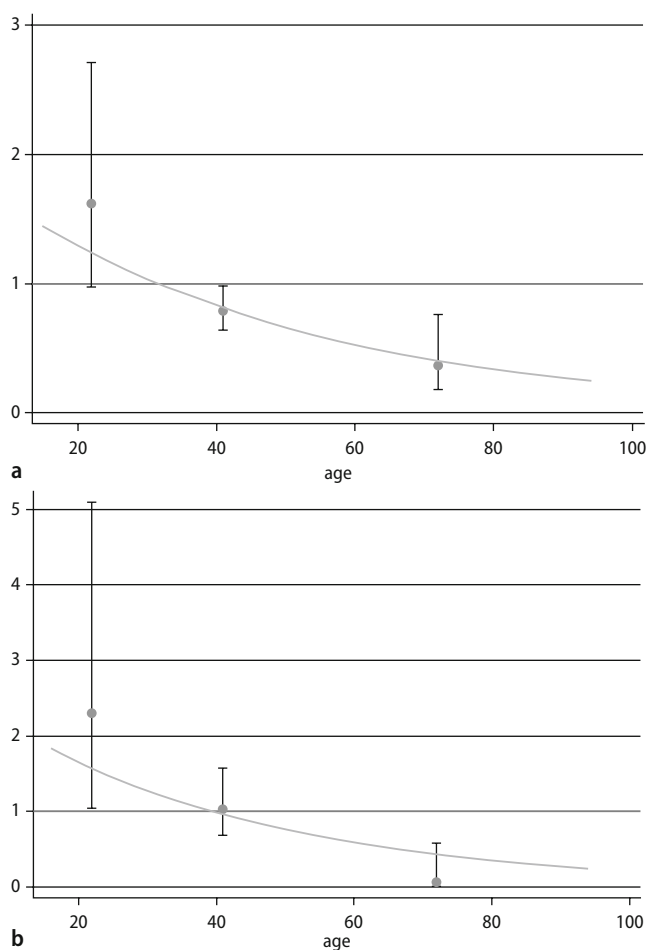
Hammad et al. [41] also investigated suicide rates in various anxiety disorders. Forty-four trials were conducted in patients with various anxiety disorders, including a total of 10,972 patients; there were two cases of suicide in these patients. In the anxiety disorder studies, the overall rate ratio of suicide for the SSRIs compared with placebo was 0.9 (0.0–71.4). The authors concluded that although neither use of placebo nor of ADs in short-term RCTs was associated with an increased risk of completed suicide among patients with major depressive disorder or various anxiety disorders, an increased risk of completed suicide in association with either drug or placebo treatment cannot be definitively excluded because of the small numbers of suicides in these trials and the subsequent lack of statistical power.

A comprehensive and methodologically differentiated meta-analysis was recently performed on this topic for a special FDA task force reviewing the relationship between antidepressant drugs and suicidality in adults [120]. This meta-analysis included the most comprehensive database of placebo-controlled trials for various indications in this research field. The trial data were submitted by the manufacturers of the 11 antidepressant drugs studied (buproprion, citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine). The primary outcome of the study was suicide-related behaviour (defined as including completed suicide, suicide attempt, preparatory acts toward imminent suicidal behaviour and suicidal ideation). Data were available from a total of 99,839 subjects in 372 trials, constituting a total of 15,505 subject years. Indications included major depressive disorder, other depression, other psychiatric disorders, other behavioural disorders and non-behavioural disorders. During the period of observation, 8 subjects committed suicide, 134 attempted suicide, 10 made preparatory actions without ever attempting suicide and 378 reported suicidal ideation without taking any action. For reasons of space it is impossible to describe all the results of the different analyses performed so that only the main results are reported here.

The estimated odds ratio for suicide-related behaviour (preparatory acts, attempts and completed suicide) associated with assignment to antidepressant drug treatment compared to placebo was 1.12 (95% CI, 0.79–1.58) for the whole dataset, indicating a non-significant risk with antidepressant drug treatment. The estimates of suicidality risk (ideation, preparatory acts, attempts and completed suicide) associated with assignment to antidepressant drug treatment compared to placebo observed from the entire dataset showed a slightly lower but not statistically significant risk with antidepressant drug treatment. Most statistical tests for differences in effect among drugs and drug classes were negative, with the exception of an indication of differences among drugs in the SSRI category. The likelihood ratio for suicidality from older drugs relative to newer drugs was 0.84 (95% CI 0.54–1.31, $P = 0.44$), i.e. suicidality was slightly but non-significantly less likely with the older than with the newer drugs. Findings were similar for suicidal behaviour of adults with psychotic disorders. The likelihood ratio for suicidal behaviour from older drugs relative to newer drugs was 0.76 (95% CI 0.38–1.50, $P = 0.43$). The odds ratios for active drug relative to placebo by different psychiatric diagnoses are not widely different from each other, but the psychiatric diagnostic categories (major depression, other depression and other psychiatric) are remarkably similar while the non-psychiatric categories appear similar to each other but distinct from the psychiatric categories. None of these differences, however, are statistically significant [120]. This confirms the calculations of Gunnell et al that the risks in controlled trials are so low that sample sizes over 200,000 would be required to detect meaningful differences.

The age ranges within the adult and paediatric studies overlap slightly and the results can be considered together to fully assess the interaction of age with AD treatment. For both suicidality and suicidal behaviour the slope of the interaction between AD treatment and age did not differ among drugs ($P = 0.22$ for suicidality and $P = 0.81$ for suicidal behaviour) nor did it differ by drug class ($P = 0.28$ for suicidality and $P = 0.78$ for suicidal behaviour). One key observation is that suicidality is positively associated with assignment to treatment with ADs in subjects under 25 years of age (Odds Ratio 1.62, 95% CI 0.97–2.71, $P = 0.07$) but negatively associated (Odds Ratio 0.74, 95% CI 0.60–0.90, $P = 0.003$) with suicidality in subjects aged 25 and older. There also appears to be a further distinction between a modest protective effect in subjects aged 25–64 (Odds Ratio 0.79, 95% CI 0.64–0.98, $P = 0.03$) and a stronger protective effect in subjects aged 65 and older (Odds Ratio 0.37, 95% CI 0.18–0.76, $P = 0.007$). Figure 1a shows these age categories graphically as well as displaying risk for suicidality as a continuous function of age. The results concerning the risks for suicidal behaviour associated with assignment to AD treatment for adult subjects with psychiatric disorders broken down by age also show a significant positive association with assignment to treatment with ADs in subjects less than 25 years of age but no overall association with suicidal behaviour in subjects aged 25 and older. There appears to be a significant protective effect of antidepressant treatment in subjects aged 65 and older (Fig. 1b).

Approximately 50% of subjects who received active drug and 40% of subjects who received placebo were designated as responders. Among those who were considered to have responded to treatment, 0.26% of all subjects with major depressive disorders and 0.13% of subjects with other psychiatric disorders displayed suicidal ideation or behaviour. For subjects considered non-responders, 1.18% with major depressive disorders and 0.55% with other psychiatric disorders displayed suicidal ideation or behaviour. The results for suicidal behaviour and suicidality odds ratios for active drug vs. placebo by subject response and age category are consistent with the idea that an increased risk of suicidal behaviour in young adults associated with AD treatment may be limited to subjects who do not show a clinical response to treatment, but this observation is far from statistically significant and would require a larger sample to make any conclusions.

There is a final minor but potentially important confounding point. Studies conducted in children have often been designed to establish 'safety' rather than efficacy, to use the summary jargon of industry. This has had the consequence that industry supported studies have failed to demonstrate efficacy because placebo response rates have been very high. In such studies, ascertainment bias relating to adverse event reporting may have been maximized, and might account for some or all of the differences between different age groups.

Altogether the results of these pooled or meta-analyses in adult psychiatric patients show a certain consistency. They generally did not find any differences between the risk of suicidal behaviour with modern ADs/SSRIs compared with placebo or standard ADs, mostly TCAs. With suicidal ideation, the results mostly show a beneficial effect. However, the meta-analysis on the database of adult psychiatric patients reported by Fergusson et al. [22] found an approximately twofold increased risk of suicidal behaviour (suicide and suicide attempts) with SSRIs compared with placebo. This increased risk was explained by a higher risk of suicide attempts, while there was no increased suicide risk. Like the other meta-analyses, Fergusson et al. [22] found no difference between SSRIs and TCAs with respect to the risk for suicidal behaviour. This finding of a generally increased risk of suicidal behaviour associated with SSRIs or other ADs was not mirrored in other meta-

Fig. 1 a Suicidality odds ratio for active drug relative to Placebo—adults with psychiatric disorders—by age [74]. **b** Suicidal behavior odds ratios for active drug relative to Placebo—preparation or worse—adults with psychiatric disorders—by age [74]

analyses on large data sets [37, 41, 120]. It is difficult to explain these contrasting results, especially since a large fraction of the data in each study will have come from the same trials! Apparently, age effects play an important modulating role, as was demonstrated in the very comprehensive and methodologically highly sophisticated meta-analysis by Stone and Jones [120]. Under treatment with ADs, younger adults (and children) appear to have a certain increased risk for suicidality in general and suicidal behaviour in particular. This levels out at the age of about 25–30 for suicidality and at the age of about 40 for suicidal behaviour, where after the risk is even reduced [21]. Since suicidal behaviour is probably more meaningfully related to suicide risk in older age groups, these findings are moderately reassuring.

Evidence from pharmacoepidemiological and cohort studies

Since the available randomised controlled efficacy studies and their meta-analyses have inherent methodological limitations, other complementary scientific approaches should be used to answer the question whether SSRIs or other ADs have an increased risk of causing suicidal behaviour. One such approach is pharmacoepidemiology, which analyses the relationship between changes in the drug treatment of depression and changes in suicide rates. Several pharmacoepidemiological studies have reported a decline in suicide rates associated with an increased prescription rate of ADs. In these studies, there was no hint of an increased risk of suicide associated with an increased prescription rate of SSRIs; SSRIs have been more and more widely used over the last 10–15 years [96]. Analyses taking into account possible confounding factors such as changes in age distribution, unemployment rate and alcohol consumption did not reach any different conclusions [10, 29, 34, 38, 55, 62, 78, 87, 108, 110].

Given the hypothesis that children and adolescents might be at higher risk, the more recent study by Gibbons et al. [30] is of special interest. This study looked at the same time window (1996–1998) and used similar methods as the earlier study by these authors [29], but focussed on children aged 5–14 and SSRI treatment. The more recent study did not find an increased risk, but found that higher SSRI prescribing was associated with lower suicide rates [30]. The most recently published study by Gibbons et al. [30] even found that in children and adolescents, the risk of completed suicide increased after the prescription of SSRIs decreased for these age groups after the FDA Black Box warning.

However, the results of these pharmacoepidemiological studies cannot rule out the possibility of an increased risk of suicide attempts with SSRIs or other ADs. They also cannot rule out an increased risk for suicidal behaviour in a few individuals with particular risk profiles. As mentioned above, these studies do not collect data on an individual but only on an aggregate level, and 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 shortcomings by assessing the risk of suicidality/suicidal behaviour in cross-sectional analyses of clinical samples. This methodological approach might be more sensitive to detecting a potential negative effect of certain groups of ADs on suicidal behaviour, although data collected in a naturalistic study are often difficult to interpret. The most relevant studies are discussed below.

Comprehensive studies of suicidal behaviour were performed based on the General Practice Research Database in the UK. The first study compared the risk of suicide in people taking ADs commonly prescribed between 1988 and 1993 [57]. Although this study found some evidence of an increased risk of suicide among people prescribed fluoxetine, it was difficult to interpret because the safety of the drug in overdose may have led to restricted prescription to people at risk of self-harm. In a subsequent study, Jick et al. [58] 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 ADs for the treatment of depression. No notable differences were found between the drugs with respect to risk for fatal or non-fatal suicidal behaviour.

Martinez et al. [82] published a nested case-control study based on the General Practice Research Database of patients with a new diagnosis of depression prescribed ADs for the first time between 1995 and 2001. This study compared the risk of non-fatal self-harm and suicide in association with the use of SSRIs and TCAs. A total of 1,968 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 0.86–1.14) and that of suicide 0.57 (0.26–1.25) in people prescribed SSRIs compared with those prescribed TCAs. 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 TCAs differed by age group (interaction $P = 0.02$). The adjusted odds ratio of non-fatal self-harm for those aged 18 or younger prescribed SSRIs compared with TCAs was 1.59 (1.01–2.50), but no association was apparent in other age groups. No suicides occurred in those aged 18 or below currently or recently prescribed TCAs or SSRIs [82]. This study has the principal methodological limitations inherent in case control studies, including the possibility of differential prescribing based on a perceived higher risk of suicidality and the absence of an untreated group for comparison.

Leon et al. [76] reported on data from the National Institute of Mental Health Collaborative Depression Study, a prospective, naturalistic follow-up of people who presented for treatment of affective disorders. The results did not support the hypothesis that fluoxetine increases the risk of suicide. Rather, there was a non-significant reduction in risk of suicidal behaviour among patients treated with fluoxetine, even though those subjects were more severely ill before treatment with fluoxetine [76].

Another cohort study was performed in New Zealand [15], following a retrospective, nested case control design. A total of 57,361 patients who received a prescription for a single AD were identified from a non-random 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 AD prescription. On univariate analysis the association, expressed as odds ratios (95% CI), with SSRIs was 2.26 (1.27–4.76) and 1.92 (0.77–4.83), respectively for self-harm and suicide. When corrected for the confounding effects of age, gender and depression/suicidal ideation there was an association between SSRIs and self-harm, odds ratio 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, 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 at 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. [119] was performed after the recent FDA warnings about potential suicidality-inducing effects of ADs. The authors used population-based data to evaluate the risk of suicide and serious suicide attempts in temporal relation to the initiation of AD treatment. Computerized health plan records were used to identify 65,103 patients with 82,285 episodes of AD treatment between January 1, 1992, and June 30, 2003. Death by suicide was identified by using state and national death certificate data. Serious suicide attempts (suicide attempt leading to hospitalization) were identified by using hospital discharge data. In the 6 months after the index prescription of AD 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 AD treatment and declined progressively after starting medication. When the ten newer ADs included in the FDA warning were compared to older drugs, an increase in risk after starting treatment was seen only for the older drugs. The authors concluded that the data did not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs. Indeed, the converse was the case: risk of serious suicide attempts fell after consultation and prescription.

Juurlink et al. [59] focussed on persons aged 60 or above in a case controlled design. Population-based coroner's records were linked with patient-level prescription data, physician billing claims and hospitalization data for more than 1.2 million Ontario residents 66 years of age and older from 1992 to 2000. For each suicide case, four closely matched comparison subjects were selected using propensity score methods. The authors determined the odds ratio for suicide with SSRIs versus other AD treatment, calculated at discrete monthly intervals from the start of treatment. During the first month of therapy, SSRI ADs were associated with a nearly fivefold higher risk of completed suicide compared other ADs (adjusted odds ratio: 4.8, 95% confidence interval = 1.9–12.2). The risk was independent of a recent diagnosis of depression or the receipt of psychiatric care, and suicides of a violent nature were distinctly more common during SSRI therapy. Numerous sensitivity analyses revealed consistent results. No disproportionate suicide risk was seen during the second and subsequent months of treatment with SSRI ADs, and the absolute risk of suicide with all ADs was low. The low absolute risk suggests that an idiosyncratic response to these agents may provoke suicide in a vulnerable subgroup of older patients [59]. This study is at variance with almost all other studies in the field and requires replication. Moreover it has no bearing on the younger age for which most concern has been expressed. The finding of more violent deaths in SSRI treated patients is not confirmed in a large Swedish database which includes the findings of post-mortem blood assay for drug levels in suicide victims [19].

In principle, a greater discrimination of putative effects might be obtained by a more focussed patient sample at higher risk of suicide and greater likely exposure to drug treatment. Inpatients with mood disorder are obviously one such high risk group. Suicide rates in patients discharged from inpatient care in Sweden were shown not to have risen in association with SSRI prescriptions [18].

Results of a more sophisticated cohort study performed in Finland were recently published [124]. In this case, a high risk group for suicidal events was

selected, i.e. people who had been hospitalized for attempted suicide and were thus at high risk for attempting suicide. Follow-up data on suicidal behaviour was collected from three large Finnish databases (National Hospital Registry, National Prescription Registry and National Mortality Registry) on 15,390 individuals who had been hospitalized for attempted suicide for any reason apart from psychosis. The mean follow-up period was 3.4 years. The follow-up data consisted of 152,587 person-years. A total of 7,136 patients were identified who had been hospitalized for attempted suicide and 602 who had died by suicide; 1,583 of the patients who had attempted suicide eventually died from other causes.

The authors applied a complex and very careful statistical methodology which took into account confounding background variables and differentiated between those patients who had never used ADs, those who had stopped using medication and those who were using medication, and reached the following main results: The adjusted relative risk for suicide with the use of any AD versus no use was 0.91. SSRI use was associated with a slightly lower, and SNA use with a slightly higher risk of suicide than no AD use, but these differences were not statistically significant. Fluoxetine use was associated with significantly decreased risk, and venlafaxine use with increased risk of suicide. In the subpopulation of subjects aged 10–19 years, 28 suicides were recorded (7 during any AD use and 21 during no AD use) [relative risk, 1.33; 95% confidence interval (CI), 0.50–3.51]. No significant differences ($P > 0.18$) were observed between the AD groups (TCA, SSRI and SNA) or specific ADs versus no use. The relative risk of suicide attempts leading to hospitalization was markedly increased during the use of all ADs when compared with no AD use. The results among the subgroup of subjects aged 10–19 years indicated a slightly higher risk increase than in the total population during the use of SSRIs. Among patients who had never used any AD, the current use of medication was associated with a markedly increased risk of attempted suicide (39%, $P < 0.001$) but, at the same time, also with a markedly decreased risk of completed suicide (−32%, $P = 0.002$) and mortality (−49%, $P < 0.001$) when compared with no current use of medication.

The authors comment that AD and especially SSRI use is associated with a marked reduction in overall mortality, mostly attributable to a decrease in cardiovascular-related deaths. In the analysis of current versus past users, it was observed that while AD use was associated with an increased risk of a severe suicide attempt, it was also associated with a markedly decreased risk of completed suicide and overall mortality. While residual confounding may have contributed to the observed increased risk of attempted suicide (in the case that patients using medication would be more severely ill and more suicidal), it is extremely unlikely that, at the same time, this residual bias could have contributed to the decreased risk of completed suicide and mortality. The authors try to explain the paradox that ADs can increase the risk of suicide attempt (meta-analysis of RCTs) and reduce the risk of suicide (epidemiological studies) by an increased risk of overdose because of easy availability of means (AD medication), resulting in an increase in nonfatal suicidal behaviour, and by a decrease in the incidence of violent and more fatal methods of suicide attempts, such as hanging and shooting [124].

The finding of Tiihonen et al. [124] that venlafaxine might have a special risk potential was supported by the study by Rubino et al. [115], which was based on a UK general practice research database. Compared with SSRIs, venlafaxine was associated with a higher risk for both suicide and suicide attempts. However, taking into account confounders in the analysis (venlafaxine patients had a higher burden of risk factors for suicide, including previous suicides and proxies for more severe or refractory depression), the size of the hazard ratios was reduced but still demonstrated a higher risk. Another recent case-control study [104] looked at suicide attempts and suicides in severely depressed adults and children who required inpatient treatment. Antidepressant treatment was not associated with suicide attempts (odds ratio 1.10; CI 0.86–1.39) or suicide (odds ratio 0.90; CI 0.52–1.55) in adults. However, there was a significant association with both suicide attempts (odds ratio 1.52; CI 1.12–2.07) and suicides (odds ratio 15.62; CI 1.65-infinity) in children and adolescents (aged 6–18).

To summarise, 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 ADs, especially no increase of suicide risk in conjunction with SSRIs. The opposite is true [96]. It is difficult to summarise the somewhat inconsistent results of the case-control and other types of clinical cohort studies. Relevant confounders like differential prescribing to patients perceived to be sicker and/or at greater risk of suicidal behaviour were not taken into account in all of these studies. When they were considered in the statistical analysis, any hints of a greater risk associated with SSRIs or ADs in general could no longer be demonstrated or were weaker. Altogether, these data have to be interpreted very carefully and cannot be seen as proof in one or the other direction.

The evidence in children and adolescents

Although this review focuses on findings in adults, the respective findings from child/adolescent psychiatry will be mentioned briefly here since 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 [66, 131]. According to Vitiello and Swedo [129], the data that formed the basis for the registration of various SSRIs, and were obtained from controlled studies performed in children and adolescents, do not allow any statistically significant conclusions to be drawn, either for an individual drug or overall. They report, for example, that proprietary data examined by the United Kingdom regulatory agency showed a slight increase in suicidal behaviour among patients who were randomly assigned to SSRI treatment compared with subjects who received placebo (3.7 vs. 2.5%). 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 [129].

A meta-analysis [53] of six placebo-controlled SSRI studies in children and adolescents published in 1994 or earlier showed no significant differences in the frequency of suicidal thoughts and attempts and self-endangering behaviour $(0.21 < P < 1.0)$ with SSRIs and placebo. There was no completed suicide in any of the studies.

Gunnell and Ashby [35] summarised the evidence from clinical trials on the adverse effects of SSRIs on suicidal behaviour in children, abstracted from information released by the Medicines and Healthcare Products Regulatory Agency. No suicides occurred in these trials. The pooled estimate of increased risk of suicidal thoughts or behaviour from these data was 1.66 (95% CI 0.83–3.50). The authors advised that this apparent increase in risk should be interpreted 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 [102]. A further factor that is difficult to control is the ascertainment bias that results from using the reported adverse effects of active treatments. Finally, 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 [79].

The ACNP Task Force Report on SSRIs and Suicidal Behaviour in Youth concluded that SSRIs and other new generation antidepressant drugs, in aggregate, are associated with a small increase in the risk of AE reports of suicidal thinking or suicide attempts in youth. However, this conclusion is limited by methodological difficulties, especially, according to Mann et al. [81], given the fact that systematic questionnaire data do not identify a risk for more suicidal ideation on SSRIs, raising concerns over ascertainment artefacts in the AE report method.

Time trends for suicide (England and Wales) [85] and non-fatal self-harm (Oxford) [44] in children and adolescents provided no consistent evidence of adverse trends paralleling increased antidepressant prescribing in the UK in the 1990s, although there was some evidence of a rise in non-fatal self-harm in young females. Furthermore, research in the United States suggests that areas with the largest increases in AD prescribing to 10–19 year olds experienced the greatest falls in suicide [105]. Olfson et al. concluded that from the population perspective, the balance of risks and benefits of SSRIs is unclear. Any AD-induced suicides may be offset by the beneficial effects of ADs 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 [43], the risk-benefit ratio 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 [35]. The most recent study by Gibbons et al. [30] indicated that in the USA and the Netherlands the suicide rate in children and adolescents increased after the prescription rate of SSRIs decreased in these age groups.

As mentioned in the introduction above, in 2004 the FDA Public Health Advisory published a statement on the risk of ADs to increase suicidality (suicidal thoughts and suicide attempts) in children or adolescents. This statement was based on the results of a joint meeting of the Psychopharmacologic Drug Advisory Committee and the Paediatric Drug Advisory Committee in 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 ADs. They also stated that there was no suicide in a huge dataset of 4,400 patients, but only suicide attempts. Even so, the FDA determined a boxed warning containing the key message that anyone considering the use of an AD in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need [20]. As a consequence of these warnings, SSRI prescriptions for children and adolescents decreased; these decreases were associated with increases in suicide rates in children and adolescents [30].

In the CHMP statement in April 2005, the EMEA took a similar course as the FDA but rather focused on the modern ADs. Beside the risk of suicidality, the statement also included the risk of hostility [16].

The FDA statement was based on a review and evaluation of clinical data [39], which was later published in 2006 [40]. Twenty-four placebo-controlled trials involving 4,852 patients were included in the publication. Sixteen trials studied patients with major depressive disorder, eight investigated other indications such as OCD or anxiety disorders. Only 20 trials

were included in the risk ratio analysis because four 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 SSRIs in depression trials as a group, and for all evaluable trials combined. There were no completed suicides in any of these trials. The overall self harm risk ratio for SSRIs 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 average risk of 'events representative of suicidality' was 4% in drug-treated patients compared to 2% in placebo-treated patients during the initial few months of treatment.

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 patient visits. They note that the suicidality signal as determined by adverse event reporting was consistent whether focusing on suicidal ideation or behaviour. Alternatively, there may be ascertainment bias implicit in taking complaints from a side effect questionnaire, where complaints of all kinds will generally be more common in drug treatment arms.

Hammad et al. [40] 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 ADs. There are also ecological data suggesting that increasing prescriptions for antidepressant drugs in adolescents are associated with a decrease in adolescent suicide [105].

The statements of the regulatory authorities were criticised as leading to therapeutic abstinence [8]. Referring to this criticism, Hammad et al. [40] pointed out that the FDA statement was not meant as a contraindication of ADs in paediatric use. Indeed, a careful consideration of the pros and cons in each individual case is necessary [119].

Higher toxicity of TCAs compared to SSRIs

A critical factor that is often ignored in the current risk/benefit discussions about ADs and suicidality is the overdose safety of ADs [63]. Consumption of a one or two week's prescription 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 ADs without any consequences [61], but venlafaxine, a SNRI, may be more toxic than SSRIs in overdose [124]. This has been demonstrated in numerous studies. Whyte et al. [133] 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 ADs 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.

Some research in this field has tried to evaluate the risk of fatal outcome in case of intoxication with individual ADs. This was performed by analysing the association between annual national death rates due to intoxication with ADs and annual national prescribing/selling rates of individual ADs. Several authors have presented the mortality statistics for ADs 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 [11, 17, 25, 50, 52, 103]. Additionally, the fatal toxicity index (FTI) was defined as the number of deaths caused by an AD 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 [51, 52], leading the authors to conclude that switching to medications with a low index would reduce the number of lethal incidents [25].

This approach was used by Henry and Cassidy over time in the UK [11, 50, 52]. The general result of these studies was that second generation ADs, including mianserin and the SSRIs, are associated with a lower rate of fatal outcome. This was interpreted as indicating a lower toxicity of modern ADs. 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 AD. In their study published in 1995, Henry et al. [52] reported that the mean annual number of deaths due to overdose with a single AD 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 TCAs as a group had a significantly higher number of deaths per million prescriptions than expected compared with all the ADs taken together ($P < 0.001$); themonoamine oxidase inhibitors as a group had a lower than expected number of deaths per million prescriptions ($P < 0.001$); the groups of atypical ADs and SSRIs 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 ADs; 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; and three of the SSRIs (fluoxetine, fluvoxamine, and paroxetine) had a lower number of deaths per million prescriptions. There is some irony in the observation that paroxetine is, on these criteria, the antidepressant drug least associated with death by overdose, when adverse publicity in the UK has reduced its prescription dramatically. 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 [52]. A subsequent study [118] using a new database of deaths from overdose and poisoning in England and Wales between 1993 and 1997 supported the view that newer ADs are less toxic in overdose than TCAs. Three recent observational studies reported that the risk of fatal overdose is greater with venlafaxine than SSRI use. It is not clear whether patient factors could account for this finding [9, 12, 101]. In the UK, venlafaxine has been selectively prescribed to a patient population with a higher burden of suicide risk factors than patients prescribed fluoxetine and citalopram. Unless baseline population differences are accounted for, observational studies that compare the risk of suicide in patients receiving these agents may produce biased results [89].

A study based on data from the Institute of Forensic Medicine, University of Vienna, Austria, confirmed the lower toxicity risk of SSRIs [25, 26] and demonstrated that TCAs were more toxic than SSRIs and other novel ADs.

The hypothesis of a stronger fatal toxicity of TCAs was supported by a study from the USA [60] in which information regarding suicide attempts and suicides by AD 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 Centres, 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 ADs, but the TCAs were associated with a higher rate of death in the event of an overdose than the newer nontricyclic ADs in both the annual report of the American Association of Poison Control Centres and the Drug Abuse and Warning Network data [60].

Similar results were also obtained from Sweden [56]. Detections of different ADs in the forensic tox-icological 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 ADs in the suicides and 1,538 in the controls. SSRIs had lower odds ratios than the other ADs.

In summary, there is strong evidence for a higher fatal toxicity of TCAs compared to SSRIs and some other modern ADs in most of the studies.

Summary

There is good data that ADs reduce depression and the suicide item on depression scales. Harmful effects of ADs on suicidality are difficult to investigate in empirical studies because of several methodological limitations. A broad scientific approach therefore has to use complementary methods to obtain the most comprehensive evidence.

One must be aware that case reports on suicidality-inducing effects of ADs should be interpreted very cautiously and different kinds of bias and misperceptions inherent in case reports should be considered carefully. Case reports can function as a source of hypotheses but cannot confirm hypotheses. If only single case data are available, the extreme uncertainty of the evidence should be addressed and relevant conclusions should be tempered.

Randomised control group studies represent the via regia to test a hypothesis. Several pooled analyses comparing industry datasets of individual ADs, mostly SSRIs, demonstrated a greater average reduction of the suicidal thoughts score with 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. These generally found no increased risk of suicidal behaviour. Several meta-analyses on large datasets of novel ADs from national drug authorities which took the suicide attempt rate or suicide rate as the outcome criterion failed to demonstrate an increased risk of suicidal behaviour during treatment with SSRIs or ADs in general. Only the meta-analysis by Fergusson et al. [22], based on a dataset from a Cochrane register, found a significantly increased risk of suicide attempts for SSRIs compared to placebo, but not different from TCAs. Age effects may play an important role, as was demonstrated in the very comprehensive and methodologically highly sophisticated meta-analysis by Stone and Jones [120]. Younger adults (and children) appear to have an increased risk for suicidality in general and suicidal behaviour in particular under treatment with ADs. This levels out at the age of about 25–30 for suicidality and at the age of about 40 for suicidal behaviour, whereafter the risk is even reduced.

This fits well with the respective findings from studies in the area of child and adolescent psychiatry. A meta-analysis by the FDA of the AD studies in children or adolescents found an increase of suicidal thoughts and suicide attempts but not suicide[20, 39, 40]. The FDA stated that this does not appear to be specific to the SSRIs.

Pharmacoepidemiological studies that applied sophisticated statistical methods to investigate the association between the prescription risks for TCAs/ SSRIs and suicide rates generally found no increased risk of suicide with ADs in general, and in particular no increase with SSRIs. The opposite is true: they generally found that a higher prescription rate of ADs, mostly SSRIs, was associated with a reduction of suicide rate. Thus if SSRIs or ADs in general do have a suicidality-inducing effect, this does not appear to translate into an increased risk of suicide; the opposite is the case, i.e. an increased prescription of ADs, preferentially SSRIs, generally leads to a reduction of suicide risk.

It is difficult to summarise the somewhat inconsistent results of the case-control and other types of clinical cohort studies. Relevant confounders like differential prescribing to patients perceived to be sicker and/or at greater risk of suicidal behaviour were not taken into account in all of these studies. When they were considered in the statistical analysis, any indications of greater risk associated with SSRIs or ADs in general could no longer be demonstrated or their size was reduced. Altogether, these data have to be interpreted very carefully and cannot be seen as proof in one or the other direction.

Differences in the fatal toxicity of ADs are of relevance for the discussions about potential harmful effects of ADs in terms of suicidality. There is clear evidence that most modern ADs, especially the SSRIs, have a lower fatal toxicity risk than the TCAs when a patient uses them to attempt suicide. In everyday clinical practice, the discussion about the possible risks of the SSRIs or ADs 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 patients with severe suicidality where the choice of a less toxic AD helps to reduce the risk of fatality if the patient should misuse the AD for a suicide attempt.

Different mechanisms could principally lead to suicidality-enhancing effects. These might, for example, be related to the pharmacological mode of action in different transmitter systems, to special pharmacodynamic properties like activating/drive-enhancing effects or to side effects like akathisia. As to special dispositions of patients, personality disturbances such as borderline personality disorder, comorbidity, nonresponse, bipolarity and other factors should be considered [2, 91, 98, 123]. When hypothesising possible mechanisms for a potentially higher suicide rate with ADs, the fact that determination of the suicide risk of an individual patient or the general suicide rate is very complex and involves the integration of different factors deserves consideration. For example, the hypothesised induction by SSRIs of suicidal thoughts or even suicidal ideation may be balanced by a lower risk of a fatal outcome of a suicide attempt with an SSRI compared to a TCA.

Beside all these considerations, the symptoms of the acute depressive episode and the risk of relapse [28, 109, 130] require an effective drug treatment that simultaneously reduces suicidal thoughts. An overcritical position which places much more importance on the risk of inducing suicidality than on the efficacy of ADs [67, 99], should be avoided [27]. One should remember that psychosocial interventions, which are often suggested as an alternative, might be ineffective under certain circumstances [127], and may even induce suicidality themselves [93, 94]. Short-term [96] and long-term data in particular underline the beneficial effects of ADs on suicidality and suicidal behaviour [1].

Of course, particularly at the start of treatment patients are often labile and it is theoretically possible that in single cases ADs, probably depending on their specific pharmacological and pharmacodynamic characteristics and in interaction with a patient's special predisposing characteristics such as personality traits and comorbidity, can induce or enhance suicidal thoughts or even reduce the threshold level for attempting or committing suicide. 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 symptoms or drug side effects that may potentially induce or enhance suicidality, a sedating or sleep-inducing comedication should be considered. It is also of greatest importance to offer the patient substantial support. Finally, it should not be forgotten that depressive symptoms and suicidal thoughts can fluctuate over the course of a day or over longer time periods. It is often difficult to follow these fluctuations carefully enough on an outpatient basis, so that inpatient treatment might be a better option for patients at an especially high risk. Treatment with ADs under inpatient conditions, which allows careful monitoring in appropriate cases, seems to be quite safe in terms of emergence or worsening of suicidality [117].

Conclusions

In surveying this important problem, three problems were posed. First, should we expect further restrictions for the use of SSRIs in adults? This is basically a political question. The cautions in children seem based less on high risk than on an over-interpretation of what suicidality actually means. Many drugs car-

rying a real risk of serious harm are marketed without black boxes, but with accepted risks balanced against known benefits. We need to be alert to the possibility that such an unusual emphasis on this aspect of drug safety for antidepressants is driven by a broader anti-psychiatry agenda. Of course, on the other hand, we can only examine the published data. There may well be unpublished data which we are not aware of but which convinced the regulatory agencies that a black box warning was necessary. Second, is there solid evidence that SSRIs carry a higher risk of inducing/aggravating suicidality compared to other ADs, especially TCAs? The simple answer appears to be 'no'. Finally, is the risk of SSRI use or the use of other ADs acceptable when balanced against the beneficial consequences of treatment with ADs according to the principles of good clinical practice? In the opinion of this expert group the answer is a clear 'yes'.

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