Eur Arch Psychiatry Clin Neurosci (2006) 256:329–343 DOI 10.1007/s00406-006-0650-x

REVIEW

Hans-Jürgen Möller

Evidence for beneficial effects of antidepressants on suicidality in depressive patients

A systematic review

Received: 1 December 2005 / Accepted: 23 January 2006 / Published online: 16 June 2006

Abstract The role of antidepressants in suicide prevention is a major public health question, given the high prevalence of both depression and depression-related suicidality. Therefore all means available should be utilised to clarify the influence of antidepressants on suicidality. This paper gives a comprehensive overview of the positive effects of antidepressants on suicidality. In the first section, principal methodological issues related to suicidology in general as well as to clinical and epidemiological studies that investigate the influence of antidepressants on suicidality are discussed. In the second section, the results of controlled clinical studies on the efficacy of antidepressants in suicidality are presented. The third section reports on the results of other types of studies, especially epidemiological studies. Altogether, there seems to be reasonable evidence from different research approaches that antidepressants are able to reduce suicidal ideation and also suicidal behaviour in depressive patients. While the evidence for the beneficial effect on suicidal ideation comes from randomised control group studies, some of which used a placebo arm, the evidence for the prophylactic effect on suicidal behaviour, especially suicide, was primarily obtained from well-designed epidemiological studies.

Key words antidepressant · suicidal ideation · suicidal behaviour

Prof. H.-J. Möller (✉)
Department of Psychiatry
Ludwig-Maximilians-University
Nussbaumstrasse 7
80336 Munich, Germany
Tel.: +49-89/5160-5501
Fax: +49-89/5160-5522
E-Mail: hans-juergen.moeller@med.uni-muenchen.de

Introduction

Suicidality, and especially suicide, is very closely associated with depressive disorders [1–6]. Given the fact that antidepressants represent an effective treatment for depressive patients, it can be hypothesised that this treatment is not only effective in reducing depressive symptoms but also in reducing suicidality associated with depression [7, 8]. This view appears to be in accordance with general clinical experience, however, from the perspective of evidence-based medicine the data do not appear to be so robust. On the other hand, there are even data which suggest the opposite, i.e. that antidepressants have a suicidality inducing/increasing effect and that this might counterbalance the positive effect of antidepressants on depressive symptoms and suicidality [9–11].

The role of antidepressants in suicide prevention is a major public health question, given the high prevalence of both depression and depression-related suicidality, [4, 6, 12]. Therefore all means available should be utilised to clarify the influence of antidepressants on suicidality. It seems impressive that hitherto there has been so much controversy about the effects of antidepressants on suicidality, which is apparently caused by a lack of convincing study results, a situation which may predominantly be due to principal methodological problems in this research field. These methodological problems will be discussed in the respective section below.

This paper gives a comprehensive overview of the positive effects of antidepressants on suicidality. In the first section, principal methodological issues related to suicidology in general as well as to clinical and epidemiological studies that investigate the influence of antidepressants on suicidality are discussed. In the second section, the results of controlled

EAPCN 650

clinical studies on the efficacy of antidepressants in suicidality are presented. The third section reports on the results of other types of studies, especially epidemiological studies. This paper does not cover the question whether antidepressants can induce or worsen suicidality. This topic will be systematically reviewed in another paper [13].

The basis for this comprehensive review was an intensive MEDLINE search for publications related to the topics antidepressants, suicide, suicidality, suicidal behaviour, suicidal ideation, aggression. Manual searches of pertinent journal article references were also performed.

Methodological problems in analysing effects of antidepressants on the suicidality of depressive patients

When considering studies performed to analyse the effects of antidepressants on suicidality, one should differentiate between several phenomena: suicidal thoughts, suicide attempts, and (completed) suicides [6]. This differentiation is apparently not always considered carefully enough in this field of research, although various indications from the literature on suicidology, among others from the area of predictor research, underline the assumption that these phenomena can only be assigned to a limited degree to the same basic concept – suicidality, although they do often appear sequentially in a patient. The risk factors for the individual phenomena are only partially congruent [14–17]. For example, simple sociodemographic data such as age and sex are of differing 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 [6]. In a recently published, huge prospective study on about 7,000 psychiatric outpatients [18] the following major risk factors for suicide were detected: depression (unipolar, bipolar), severity of depression, suicidal ideation, hopelessness and unemployment. Other known risk factors for suicide, found in prospective studies, are schizophrenia, substance abuse, personality disorder, family history of mental disorder, history of attempted suicide, male gender, status of being widowed or divorced [19].

When analysing the effects of antidepressants on suicidality the differentiation between different phenomena of suicidality should be considered. Also, it should be attempted to disentangle drug effects on suicidality itself from effects on drive, autoaggression and impulsive behaviour, which can themselves influence suicidal behaviour [10, 11]. Finally, major predictors/risk factors for suicidality should be carefully considered.

Methodological problems of control group studies on suicidality

If one wants to investigate the question whether an antidepressant generally has a special influence on the risk for suicidal behaviour (suicide attempts and suicides), one has to put the number of events in relation to the number of cases treated and compare the resulting ratio with the risk rates known from the literature. However, when doing this a selection bias in the different samples must be carefully considered. For this reason, open studies can easily lead to misinterpretations and are only of limited value. Randomised, control group studies, especially when placebo controlled, seem to be the best basis for statements about the suicide risk of certain antidepressants.

However, the results of such control group studies also have to be viewed critically under consideration of methodological pitfalls inherent in the design of such studies. The low basal prevalence of suicidal behaviour has the consequence that, for principal reasons, it is almost impossible to perform a control group study with an adequate statistical power to differentiate between the outcome results of two treatment groups as the number of these events is small in a medium-sized and even in a large control group study. This could possibly be overcome by an enriched sample design, however, most of the respective control group studies on antidepressants do not deal with samples in which the symptom suicidality/suicidal thoughts is enriched. The opposite is true: most studies exclude at least patients with serious suicidal thoughts. The principal ethical aim, i.e. to avoid harm to the patients, conflicts with the scientific objective of such studies. Thus the ideal control group design to answer the question whether antidepressants reduce suicidality cannot be realised for ethical reasons. The consequence of this might be that any indications of efficacy do not reach statistical significance and, in addition, are far removed from the actual efficacy in real life conditions. The exclusion of patients at higher risk for suicidality might also have other consequences, e.g. that a potential suicidality-increasing effect, and in particular an increased rate of suicide attempts or suicide, cannot be proven. The problem of a low base rate of the risk of suicidal behaviour due to selection processes is increased by other factors. Special risk conditions such as comorbidity, including comorbidity with accentuated personality traits, or even personality disorders, are mostly exclusion criteria. These comorbidity conditions can increase the risk of suicidality itself in a direct way or indirectly via other mechanisms such as changes in impulsivity or paradoxical drug effects. The likelihood of proving a special influence on suicidal behaviour is thus significantly reduced from the start. Furthermore, during the study careful attention is paid to the early recognition of suicidal crises,

which are then immediately compensated for through early intervention, e.g. with additional medication or psychotherapeutic approaches. The problems associated with patient selection mentioned above are especially relevant for placebo-controlled studies in which exclusion criteria for patients at risk of suicide are even stricter than for active comparator studies.

For several reasons, attempted or completed suicides are so rare in these studies (mostly below 2%) that in view of the group sizes in such antidepressant studies (an average of 50–200 patients per group) no significant differences between the two comparative substances can be expected. At the most meta-analyses of a larger number of studies can allow relevant statements to be made. In order to increase the chance of obtaining statistically significant results in such clinical, control group studies, or in meta-analyses of these studies, suicide attempts and suicides are often combined to give one outcome measure. However, this approach does not do justice to the fact that such a combination is not meaningful from a suicidological standpoint, as mentioned above.

The problem of the too low event rate for suicidal behaviour has the consequence that most control group studies designed to evaluate the suicidality-reducing effects of antidepressants use the decline of suicidal thoughts as a certain type of proxy-outcome criterion for suicide attempts or suicidal events. On the other side, control group studies that try to determine the respective risk of antidepressants include suicidal thoughts as an additional outcome criterion in order to increase the chances of finding a signal. However, as mentioned above, suicidal thoughts are only associated to a certain degree with suicide attempts and suicide, and can only be interpreted extremely cautiously as a surrogate parameter for suicidal events.

Another problem is that published data from controlled studies on the question of the effects of antidepressants on suicidality in depressed patients mostly stem from clinical studies of antidepressants whose primary objective was to prove the antidepressant effect of the respective substance. In other words, these studies were not primarily designed to investigate the influence of the antidepressant on suicidality. Beside the methodological problems discussed above, i.e. that patients with a relevant risk for suicidality were excluded from these studies, a further weakness is that special rating scales for suicidality were not applied. For this reason, only limited relevant information is available for evaluations, mostly one item of the applied depression scale. The analyses therefore mostly cover suicidal thoughts as this outcome criterion represents the only parameter that occurs frequently enough to allow statistical comparison between groups under the conditions of a randomised, control group study.

Prospective, randomised, control group studies, designed to study the effects of antidepressants on suicidality in a sample enriched with respect to the prevalence of suicidality, could be a way to overcome the problems mentioned above, as suggested by an ACNP consensus group [20]. However, this might be highly problematic for ethical reasons, and a study of this kind does not appear to have been performed hitherto.

Due to these limitations of controlled clinical studies, other 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 community-based interventions and also clinical experience with single cases.

Methodological problems of epidemiological studies and other types of observational studies

Epidemiological studies that analyse the relationship between changes in drug treatment of depression and changes in suicide rates are important as such a complementary approach. However, it is necessary to take into account several confounding factors that might influence the suicide rate, such as age distribution, alcohol consumption, unemployment rate, etc. Thus, meaningful results can only be obtained by complex statistical analyses.

Although there might be problems associated with a differentiated interpretation of the results from epidemiological studies in this field, generally the epidemiological methodology has reached such an excellent standard that complex statistical analyses, which take into account the most relevant confounding factors, can generate very reliable results.

However, in addition to this more general view, the situation is also quite complex from a pharmacological perspective. For example, the suicide rate has to be seen as a net effect of different pharmacological factors and is not necessarily closely associated with the rate of suicide attempts. If only suicides by drug intoxication are counted, it may be the case, for example, that a highly toxic antidepressant A is characterised by the fact that a high proportion of suicide attempts with this antidepressant have a fatal outcome. The number of suicides with this drug would thus be highly correlated with the number of suicide attempts with this antidepressant. The opposite situation is found if an antidepressant B is very safe in case of overdose: the number of suicide attempts with this antidepressant B might not be correlated at all with the number of suicides with this drug.

A further pharmacological scenario should be reflected on in this context. Antidepressant A does not increase the rate of suicide attempts, but leads to a fatal outcome (suicide) in case of attempted suicide. Antidepressant B increases the risk of suicide attempts and, although the intoxication with this drug does not have a fatal outcome, it increases the rate of

suicide due to the fact that patients use other effective methods to commit suicide. All these aspects have to be taken into consideration. If only suicides with this antidepressant are counted, the latter effect would not be detected.

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

Date from complex community-based intervention programmes such as awareness and education campaigns, which focus on improving diagnosis and treatment of depression, can also contribute to the evaluation of the role of antidepressants in terms of suicidality. Depending on general aspects of the design, and especially on the degree of control for time-related effects or other confounding factors, the findings can be seen to be more or less robust.

The principal limitations of case reports

For most clinicians, clinical experiences with individual patients in particular lead to the assumption of a positive effect of antidepressants, not only in terms of depressive symptoms but also suicidality. However, this clinical experience is generally not seen to prove the hypothesis that antidepressants can reduce suicidality [10]. On the contrary, single case experiences are generally seen to be much more important in the detection of suicidality-inducing effects of antidepressants. Given this asymmetric situation of argumentation it appears important to discuss the validity of the single case approach in principal. It is very important to note that single case experiences can only lead to the formulation of a hypothesis, but can never be regarded as giving adequate proof of such a hypothesis. It can only be assumed that there is a 'real finding' if such a hypothesis is validated in a randomised, control group study or in other kinds of controlled approaches such as quasi-experimental statistical analyses of huge data sets, e.g. epidemiological case control studies.

In the face of all these problems clinical experience from routine daily care, i.e. clinical single case observations, is of limited relevance for the analysis of the effects of antidepressants on suicidality in depressive patients. Such uncontrolled experiences are very error-prone and can therefore only be accepted to a limited degree as a method of obtaining proof.

Antidepressants reduce suicidal thoughts in depressive patients: clinical experience and data from randomised control group studies

As mentioned above, clinicians assume that antidepressants not only reduce depressive symptoms but also the associated suicidality. This clinical experience is confirmed at least in terms of suicidal ideation by the results of controlled antidepressant studies which show that, if the depression subsides during treatment with antidepressants, the suicidal thoughts are usually also reduced or disappear.

However, in the early publications on antidepressants there are hardly any special studies on this topic. Much more interest in exploring this matter was shown later on in the context of the question whether certain antidepressants reduce suicidal thoughts more quickly or effectively, particularly after the advent of the selective serotonin reuptake inhibitors (SSRIs).

Montgomery et al. were the first group to compare the antisuicidal effects of the classical tricyclic antidepressant (TCA) amitriptyline with those of two second generation antidepressants, maprotiline and mianserine, in a pooled analysis of three small, control group studies [21]. Mianserin thereby showed a significantly greater reduction of suicidal thoughts than amitriptyline and maprotiline, which showed approximately equal effects. The difference in the effects on suicidal thoughts were not explained by the difference in the global antidepressive efficacy.

Subsequent to the finding by Asberg's research group [22, 23] that there is a decreased level of hydroxyindole acetic acid (the first metabolite of serotonin) in the CNS of patients after suicide attempts, especially in cases of particularly strong autoaggressive suicide attempts, the serotonin deficiency hypothesis of suicidality was developed. This hypothesis was subsequently supported by further data, although conflicting findings were later published [24–26]. In relation to this hypothesis it appeared of interest to investigate whether the SSRIs are superior to other antidepressants in the treatment of suicidal thoughts. The first evaluation of this question was presented by Montgomery et al. [27]. In accordance with the hypothesis, Montgomery's group found that suicidal thoughts subsided faster with the SSRI zimelidine than with the TCA amitriptyline at doses that were comparable with respect to the global antidepressive effect [27]. This double-blind study was performed in 40 patients with well-defined 'endogenous' depression. It is unusual for a trial of this size to reveal significant differences between antidepressants on the individual items of a depression scale, and thus this might be seen as an indicator of a strong effect. Another study [28] in 60 patients who fulfilled Research Diagnostic Criteria [RDC; [29]] for either endogenous depression or chronic dysthymic disorder revealed similar results. The patients received under double-blind conditions either the SSRI

citalopram or mianserin (a tetracyclic antidepressant). When compared with mianserin, citalopram was found to exert relatively greater effects on reducing suicidal thoughts as estimated by the Montgomery–Asberg Depression Rating Scale (MADRS) item.

Two of the studies that tested whether SSRIs have a faster/stronger effect on suicidality used a placebo-controlled design. In a double-blind, control group, three-arm study fluvoxamine was compared with imipramine and placebo [30] (see also [31]). There was a significantly faster reduction of suicidal thoughts in the fluvoxamine group, although the antidepressive effects were the same in both active substance groups. Both antidepressants were superior to placebo with respect to global treatment success and improvement of suicidal thoughts, not only in the sense of a faster reduction but also a greater reduction at the end of the 4 weeks' treatment. A further double-blind, control group study [32] revealed evidence for a beneficial effect of fluoxetine in reducing suicidal thoughts. Eighty-one patients who fulfilled RDC criteria for major depression received either fluoxetine, mianserin or placebo. Suicidal thoughts were reduced to a significantly greater degree with fluoxetine than with either mianserin or placebo.

These findings of a special advantageous effect of SSRIs on suicidality could not be confirmed in a multicentre study in which paroxetine was compared under double-blind conditions to amitriptyline [33]. This study involving 223 patients found no difference between the two treatment groups concerning the speed or size of the reduction of suicidal thoughts. However, both suicidal thoughts and depressive symptoms were reduced under treatment with either paroxetine or amitriptyline.

A pooled analysis of all data from control group studies of the SSRI fluoxetine, involving a total of 1765 patients treated with fluoxetine, 569 with placebo and 731 with TCAs, found no indication for an advantage of fluoxetine over the comparative standard antidepressants in the reduction of suicidal thoughts. However, of most relevance in the context of the general discussion of this paper is that suicidal ideation improved significantly more with fluoxetine than with placebo (72.0% versus 54.8%, $P < 0.001$) and was similar to the improvement with tricyclic antidepressants (72.5% versus 69.8%, $P = 0.294$) [34]. It is important to underline that in terms of suicidal behaviour (suicide attempts and suicide) there is no relevant difference: the pooled incidence of suicidal acts was 0.3% for fluoxetine, 0.2% for placebo and 0.4% for tryicyclics. The slight numerical differences were not statistically significant. If only placebo-controlled fluoxetine studies were included in the pooled analysis, the rate in the fluoxetine and placebo groups was the same: 0.2% [34].

In a pooled analysis of the effects of paroxetine on suicidal thoughts and attempts, Montgomery [35] focussed on the MADRS suicidality item, which measures the thoughts independently of any suicidal act, while the commonly used Hamilton Depression Rating Scale (HAMD) suicidality item is a composite of both thoughts and acts. However, in most of these studies also the HAMD item basically covers suicidal thoughts, given the fact that suicidal events are extremely rare in clinical trials on antidepressants. In Montgomery's pooled analysis of the MADRS suicidal thoughts item comparing paroxetine ($n = 1510$), placebo ($n = 459$) and active control ($n = 454$), there was significantly greater mean improvement in the paroxetine-treated group compared with the active control-treated group at weeks 1, 3 and 4 ($P < 0.01$), and a significantly greater improvement than in the placebo-treated group at weeks 1, 2, 3, 4 and 6 ($P < 0.0001$), [35]. The improvement in the active control group was better than in the placebo-treated group at weeks 1 ($P < 0.05$) and 2 ($P < 0.01$). The MADRS was not used in all studies so the HAMD suicidality item pooled analysis was based on a somewhat larger group and this, too, found that both paroxetine and active comparators were associated with significantly greater improvement than placebo on the suicide item, with a significant difference at weeks 1, 2, 4 and 6 ($P < 0.05$). The improvement on paroxetine was greater than that on comparators at weeks 2, 4 and 6 but the difference was not significant [35]. More or less the same results were also obtained in the pooled analysis performed by Lopez-Ibor [36] using nearly the same data pool of paroxetine comparator studies (Fig. 1), but this paper goes beyond the scope of suicidal ideation by including in addition an analysis of attempted suicides and suicides which were reported as adverse events. The change in the HAMD suicidality item score over time showed that paroxetine and the active control were significantly superior to placebo in reducing suicidal thoughts (and behaviour) from week 1 onward. In terms of frequency of attempted suicide and suicide, documented as adverse events, there were no statistically significant differences between the groups. The frequencies for suicides were as follows: 0.17% for par-

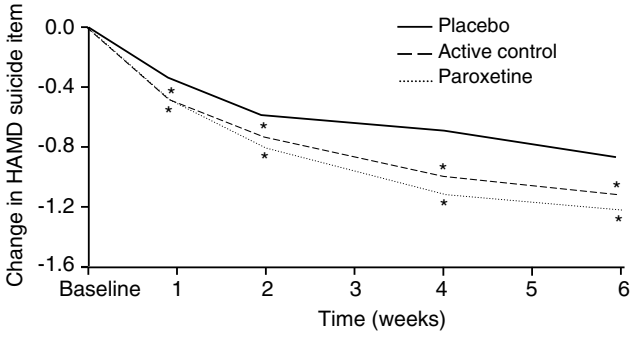

Fig. 1 Change in HAMD suicide item score over time [36]. *$P < 0.05$; paroxetine/active control versus placebo

oxetine, 0.26% for active control and 0.36% for placebo; the frequencies for attempted suicides were 1.3% for paroxetine, 1.0% for active control and 1.1% for placebo.

A pooled analysis was performed on suicidality data for the escitalopram database (n = 2277 for escitalopram; n = 1814 for placebo) from clinical trials on depression [37]. With regard to suicidal thoughts, as measured on item 10 (suicidal thoughts) of the MADRS (Major Depressive Disorder studies, N-ITT = 1939), the mean value over time demonstrated a significant reduction of suicidal thoughts versus placebo at all time points (weeks 1 through 8, $P < 0.05$ and $P < 0.001$, respectively).

Altogether these findings supply some evidence that antidepressants are able to reduce suicidal thoughts in depressive patients. This effect is associated with the global antidepressive effect. However, when comparing different antidepressants it appears that, although they show the same global antidepressive efficacy, there might be differences in their speed or capacity to reduce suicidal thoughts. This point was a particular focus of discussion for the SSRIs, but the hypothesis that SSRIs have a faster/stronger effect on suicidal thoughts could not be confirmed when the results of all randomised, control group studies were viewed collectively, although some individual studies point in this direction.

One might hypothesise from a clinical perspective that the beneficial effect on suicidal ideation has consequences for the prevention of suicide attempts or even completed suicide. However, empirical data from randomised controlled studies, and even the pooled analyses of fluoxetine or paroxetine comparator trials, give no support to this hypothesis. Methodological limitations may not allow this question to be addressed in an adequate way, as mentioned above. The extremely low basal rate of the risk of suicide attempts, and especially completed suicide, is a limiting factor in short-term studies of antidepressants. Even meta-analytical approaches on huge data sets are apparently not able to overcome the respective power problem of individual studies. Khan et al. [38–40] analysed several FDA databases on randomised, placebo- and/or active comparator-controlled trials on new antidepressants, mostly SSRIs. The analysis of this huge database did not find any significant differences between placebo, active comparator or investigational antidepressants in the rates of attempted or completed suicide. In a similar meta-analysis [41], all randomised and placebo-controlled, double-blind, short- and long-term studies of an antidepressant that were part of a registration dossier that was submitted to the Dutch regulatory authority between 1983 and 1997 were reviewed for attempted suicide. In addition, all long-term, placebo-controlled antidepressant studies that were conducted in the last decade in patients with major depression were identified by a Medline search and assessed for attempted suicide. The analysis of this huge database was unable to demonstrate a significant difference in the risk of suicide attempts between active compounds and placebo. When interpreting the results of the long-term studies it should be considered that even under these long-term conditions (the duration of most of the studies was one year), the basal rate of suicide attempts was low, i.e. up to 0.2%.

A recent meta-analysis [42] evaluated the full datasets from the studies, published and unpublished, supplied to the UK regulatory authority, the MHRA, by all the pharmaceutical companies producing SSRIs. The analysis of these data from 477 studies including 40,826 patients found a slight, non-significant protective effect of SSRIs on suicide compared to placebo [odds ratio (OR) 0.85, confidence interval (CI) 0.20 to 3.40]. This meta-analysis shows again that the risk of SSRI-related suicide is low in these clinical trials, and more or less not different to placebo. A similarly slight, non-significant protective effect of SSRIs on suicidal thoughts reported as an adverse event (OR 0.77, 0.37–1.55) was found. The meta-analysis of non-fatal self-harm (very broadly defined) found a slight, non-significant higher risk for SSRIs (OR 1.57, 0.99–2.55). These data, despite the very large numbers of patients included, do not give clear answers but do identify that there is a small risk of suicide and suicide events when depression is treated with either SSRIs or placebo, without showing a clear protective effect of SSRIs and even suggesting a slight but not significant risk for SSRIs to induce non-fatal self-harm.

The most comprehensive meta-analysis in this field was recently published by Fergusson et al. [9], based on a Medline search and on the Cochrane Collaborations Register of Controlled Trials, produced by the Cochrane Depression, Anxiety and Neurosis Group. In order to be included studies had to randomised, controlled trials comparing an SSRI with either placebo or an active, non-SSRI control for any clinical condition (not only for depression!). The latter were divided into the group of tricyclics and the group with therapeutic interventions other than tricyclics (including moclobemide, maprotiline, mianserin and psychotherapy!), a very heterogeneous group. Seven hundred and two trials with 87,650 patients were primarily included, but only a total of 345 trials representing 36,445 patients reported the numbers of suicidal acts (143 in total) and were included in the analysis. In contrast to the 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. This meta-analysis found no indication of a beneficial effect of antidepressants, but an increase of "suicide attempts" in the SSRI group compared to placebo.

There were no differences in terms of "suicide attempts" between SSRIs and TCAs.

Altogether these findings from pooled analyses/meta-analyses of results of randomised, controlled, short-term and long-term trials (mostly only up to 1 year) do not support the hypothesis that antidepressants reduce attempted or completed suicide. This astonishing result, which appears to contradict general clinical experience, together with the findings from randomised, controlled trials that antidepressants reduce suicidal thoughts, might be due to methodological pitfalls such as a low basal rate of the outcome criteria suicide attempts or suicide and recruitment of a low risk population. The results of the meta-analysis by Fergusson et al. [9] that, in contrast to the general expectations, there might be an increased risk of suicidal behaviour as a consequence of treatment with antidepressants requires further discussion [13].

Results from epidemiological, awareness and follow-up studies

Interesting data demonstrating the capacity of antidepressants to reduce suicidal behaviour were obtained in recent years from the epidemiological field. In face of the situation that it appears to be extremely difficult to prove the antisuicidal effect of antidepressants in randomised, control group studies – see the above discussion about the methodological problems of such studies – such a naturalistic approach seems to be one of the best ways to find at least some confirmation. It is backed up by data from awareness and follow-up studies. However, naturalistic studies are always difficult to interpret due to several potential confounding factors, which have to be considered carefully.

Results of epidemiological studies

The prescription rate of antidepressants has increased in several countries in the past decade, partly associated with the fact that modern antidepressants are better tolerated and therefore easier to handle in the everyday routine care situation, especially in primary care. This increased prescription of antidepressants offers the possibility of a quasi-experiment in which the suicide rates at the time of a higher and lower prescription rate can be compared.

Isacsson collected and carefully analysed such data in a study on suicide rates in Sweden and other Scandinavian countries [8]. He took into account relevant confounding factors which might explain the change in suicide rates, like unemployment rates and alcohol consumption. However, this was not performed using complex statistical procedures but only by looking at the development of each of these variables over time. The author hypothesized, based on research until 1991, that a five-fold increase in the use of antidepressants might reduce Swedish suicide rates by 25%. A subsequent 3.5-fold increase in the use of antidepressants provided a 'natural experimental situation' for prospectively testing this hypothesis. Swedish statistics on suicide, use of antidepressants, unemployment and alcohol consumption were obtained for the years 1978–1996 and time-series of the latter variables were compared with suicide rates. Demographic subgroups regarding age, gender and county were analysed. In addition, suicide rates in other Scandinavian countries were also compared with the use of antidepressants in these countries. The suicide rate in Sweden decreased by 19% in parallel with the increased use of antidepressants, from 23.3 suicides per 100,000 inhabitants in 1991 to 18.8 in 1996 ($\rho = -0.90$, $P < 0.05$) (Fig. 2). The annual differences in suicide rate and use of antidepressants did not correlate with each other, but the differences between the consecutive 3-year periods did ($\rho = -0.90$, $P < 0.05$, one-tailed) (1979–1981, 1982–1984, 1985–1987, 1988–1990, 1991–1993, 1994–1996). Considering subgroups, in Sweden during 1990–1996 there were no demographic groups with regard to age, gender or county in which the suicide rate decreased in the absence of an increased use of antidepressants. In women under 30 and over 75 years of age, however, and in four of the 23 counties (Jönköpring, Östergötland, Örebro and Västerbotten counties), suicide rates remained unchanged despite an increased use of antidepressants. Female suicides in these age groups, and suicides in these four counties, constituted 8% and 14% of all suicides during the period. Inverse correlations between the use of antidepressants and suicide rates were also seen in the three other Scandinavian countries, Denmark ($\rho = -0.94$, $P < 0.01$), Norway ($\rho = -0.87$, $P < 0.05$) and Finland ($\rho = -1.00$, $P < 0.01$) during 1990–1996 (Fig. 2). There was no consistent correlation in Sweden, 1978–1996, between suicide rates and alcohol consumption, or between suicide rates and unemployment rates (Fig. 2) [8]. In this epidemiological study it appears that the increased use of antidepressants is one of the contributing factors to the decrease in the suicide rate.

A similar study by Carlsten et al. [43] confirmed this finding for Sweden. This group covered the years 1977–1997 and found that not only did suicide rates decrease over the whole study period, but the rate of decline accelerated after the introduction of the SSRIs in 1990.

Another study of this type that also confirmed these results was performed in Hungary, a country known for its traditionally high suicide rate [44]: The suicide rate of Hungary (which was the highest in the world until 1992) has shown a steady decline from 45.9 per 100,000 in 1984 to 32.1 in 1998, a fall of more than 30%. This decline was greater after 1990, when

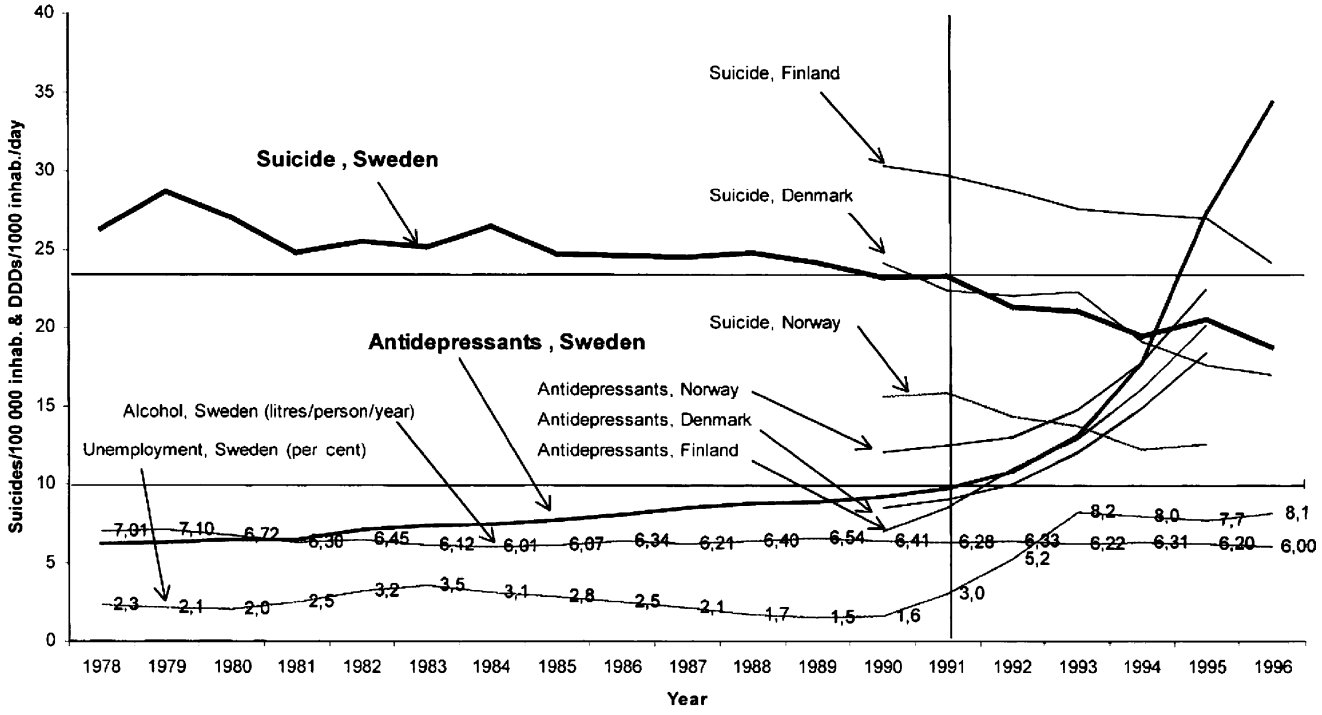

Fig. 2 Correlations with Swedish suicide rates in the retrospective analysis of 1978–1991. Two-tailed tests: antidepressants: $\rho = -0.85$, $P < 0.01$; unemployment: $\rho = +0.25$, NS; alcohol: $\rho = +0.30$, NS. Correlations with suicide rates in the prospective analysis of 1992–1996. One-tailed tests: antidepressants: $\rho = -0.90$, $P < 0.05$; unemployment: $\rho = -0.25$, NS; alcohol: $\rho = +0.70$, NS [8]

the rate was 39.9 per 100,000 and when the political and economic changes in Eastern Europe began. This marked decrease in suicide mortality in Hungary happened in spite of the fact that between 1989 and 1996 there was a sixfold increase in unemployment (from 1.7–10.9%), a 25% rise in official estimates of alcoholism rates and a 21% increase in divorce. However, the number of outpatient psychiatric departments increased from 95 in 1982 to 136 in 1998, the number of psychiatrists increased from 550 in 1986 to 850 in 1998, and the number of emergency (SOS) telephone services also increased from 5 to 28 during the same period. More extensive medical training on depression and suicide was followed by a marked rise in the use of antidepressants, mainly SSRIs, after 1990, from 2.6 DDD/1000 people/d in 1984 to 12.0 in 1998, which is an approximately fivefold increase. In other words, despite the adverse changes in key social-psychiatric suicide risk factors, a fivefold rise in the use of antidepressants, which is interpreted as a reflection of the widespread and improved care for psychiatric and particularly depressed patients, was followed by a 30% decline in the suicide rate in Hungary between 1984 and 1998 [45]. To obtain further proof that antidepressants are a relevant influencing factor for the decrease of suicide rates in comparison with other potentially relevant psychosocial factors, Rihmer focussed in another study on the seasonality of suicide [46].

Grunebaum et al. [12] presented the results of a methodologically very sound analysis of the US-American data for the years 1985–1999 that took into account unemployment and alcohol consumption as confounding factors in a multivariate approach. The relationships between the suicide, antidepressant prescription, unemployment and alcoholic beverage consumption rates were studied using generalized linear models. Suicide rates by antidepressant overdose were compared in SSRIs and TCAs. From 1985 to 1999, the suicide rate fell 13.5%, with a greater decline among women, and antidepressant prescription rates increased over fourfold, with the increase mostly due to SSRIs. Prescription rates for SSRIs and other second-generation antidepressants were both inversely associated with suicide rates ($P = 0.03$ and $P = 0.02$, respectively). In a multivariable analysis adjusting for unemployment and alcoholic beverage consumption rates, SSRI antidepressant prescription rates remained inversely associated with the national suicide rate ($P = 0.03$). The authors came to the conclusion that the decline in the national suicide rate (1985–1999) appears to be associated with greater use of non-tricyclic antidepressants. The authors concluded that treatment of a greater proportion of mood disorders with SSRIs and other second-generation non-tricyclic antidepressants may further reduce the suicide rate [12].

A similar study on suicide data from the USA performed by Gibbons et al. [4] obtained somewhat more differentiated results. This methodologically sophisticated study focussed on the years 1996–1998 and categorised the national county-level suicide rates

according to age, sex, income, race and antidepressant prescription rates (expressed as number of pills prescribed). The overall relationship between antidepressant medication prescription and suicide rate was not significant. Within individual classes of antidepressants, prescriptions for SSRIs and other new-generation non-SSRI antidepressants (e.g. nefazodone hydrochloride, mirtazapine, bupropion hydrochloride and venlafaxine hydrochloride) were associated with lower suicide rates (both within and between counties). A positive association between TCA prescription and suicide rates was observed, i.e. higher TCA prescription rates were associated with a higher suicide risk. Results were adjusted for age, sex, race, income and county-to-county variability in suicide rates. Higher suicide rates in rural areas were associated with fewer antidepressant prescriptions, lower income and relatively more prescriptions for TCAs. The authors drew the following conclusions: "The aggregate nature of these observational data preclude a direct causal interpretation of the results; a high number of TCA prescriptions may be a marker for those counties with more limited access to quality mental health care and inadequate treatment and detection of depression, which in turn lead to increased suicide rates; by contrast, increases in prescriptions for SSRIs and other new-generation non-SSRIs are associated with lower suicide rates both between and within counties over time and may reflect antidepressant efficacy, compliance, a better quality of mental health care, and low toxicity in the event of a suicide attempt by overdose" [4]. It should be noted that in their interpretation of the results, Gibbons et al. do not take into account the higher toxicity of TCAs, which might result in an increased fatal outcome in case of attempted suicide.

The study by Hall et al. [47] is also of great interest due to its differentiated results. This study generally found similar results for Australia, although they were differentiated for certain age groups. The analysis is based on trends in antidepressant prescribing and suicide rates for Australia for the years 1991–2000. Alcohol consumption and unemployment were not included in the calculations. It is only mentioned that per capita alcohol consumption remained stable in most of the respective time periods, and unemployment rate even increased and therefore cannot explain the decreased suicide rate. The study found that while overall national rates of suicide did not fall significantly, changes in suicide rates and exposure to antidepressants in Australia for 1991–2000 were significantly associated. This suicide-decreasing effect was most apparent in older men and women, while there was an increase in younger adults. In both men [$r(s) = -0.91$; $P < 0.01$] and women [$r(s) = -0.76$; $P < 0.05$] the higher the exposure to antidepressants, the larger was the decline in rate of suicide. The authors propose that the increase in antidepressant prescribing may be a proxy marker for improved overall management of depression. If so, increased prescribing of SSRIs in general practice may have produced a quantifiable benefit in population mental health [47].

In the study by Hall [47], the group with the largest increase in antidepressant prescription showed the largest reduction or lowest increase in suicide rate. A similar relationship was found in the USA for children and adolescents [48]. This study divided up regions according to postcodes and found a significant adjusted negative relationship between regional change in antidepressant medication treatment and suicide during the study period. A 1% increase in adolescent use of antidepressants was associated with a decrease of 0.23 suicide per 100,000 adolescents per year ($\beta = -0.023$, $t = -5.14$, $P < 0.001$). In stratified adjusted analyses, significant inverse relationships were present among males ($\beta = -0.032$, $t = -3.81$, $P < 0.001$), youths aged 15–19 years ($\beta = -0.029$, $t = -3.43$, $P < 0.001$), and regions with lower family median incomes ($\beta = -0.023$, $t = -3.73$, $P < 0.001$). With its focus on children and adolescents, these results should be taken seriously into account in the current discussion about the benefit/risk ratio of antidepressants in the treatment of depressive children or adolescents [49].

In their study on antidepressant prescribing and suicide rate in Northern Ireland, Kelly et al. [50] found in the "older" group of the population (30 years and above) an association between increased antidepressant prescribing and reduction in suicide rate over the 10 years of the study, while there was no association for the "younger" population (<30 years). The following confounders, among others, were considered in the applied linear regression model: unemployment rate and household alcohol expenditure.

In order to give a balanced overview it should be mentioned that two studies were unable to support the findings of an association between an increased prescription rate of antidepressants and a decreased suicide rate [51, 52]. However, the negative result of the Italian study [51] can possibly be explained by quite a low prescription rate of antidepressants in general, and the Icelandic study [52] by a low rate of suicides in general.

In a recent paper, Rihmer [53] comments critically on van Praag's opinion [54] that antidepressants do not reduce suicide rates. His first criticism is that van Praag shows the suicide rates only between 1980 and 1995 and does not consider the figures already reported for the years 1998–2002. Second, Rihmer states that van Praag has completely neglected almost all the countries which showed the greatest decline in their suicide rates between 1980 and 1998/2002. Table 1 shows the national suicide rates of the 10 countries with the greatest decline in their suicide rates between 1980 and 1998/2002. In the majority of these countries (eight of the 10) the peak was in 1980 or 1985, and nine of them had their lowest rate in 1998/2002.

Table 1 National suicide rates of the 10 countries with the greatest decline in the suicide rates between 1980 and 1998/2002 [53]

Country	1980	1985	1990	1995	1998/2002	Difference (peak minus 1998/2002)
1. Denmark	31.6	27.9	23.9	17.7	14.4	−54%
2. Hungary	44.9	44.4	39.9	32.9	28.0	−38%
3. Germany	20.8	16.5	17.8	15.8	13.6	−35%
4. Austria	25.7	27.7	23.6	22.2	18.3	−34%
5. Estonia	36.7	22.3	27.1	40.1	27.5	−31%
6. Switzerland	25.7	25.0	21.9	20.2	18.1	−30%
7. Sweden	19.4	18.2	17.2	15.3	13.8	−29%
8. Finland	25.7	24.6	30.3	27.2	22.5	−26%
9. Czech Rep.	–	20.9	19.3	17.5	16.1	−23%
10. France	19.4	22.5	20.0	20.6	17.5	−22%

Rihmer writes "No sophisticated statistical analysis is necessary to accept that the national suicide rates declined dramatically in these countries, and particularly in those which had previously had the highest suicide rates in the world (Hungary, Denmark, Estonia, Austria, Switzerland, Sweden, Finland, etc.). The 54% decrease in Denmark as well as the 30–38% decline in Switzerland, Estonia, Austria, Germany and Hungary is really impressive; a huge increase of antidepressant prescription in the last 10–15 years has been reported from Denmark, Hungary, Sweden and Finland [8, 44, 54a). There is no doubt that a similar decrease is present in the other six countries" [53].

Considering all the above, it is evident that an increased utilisation of antidepressants, especially SSRIs, was accompanied by a relevant decline of national suicide rates in several countries, particularly in those where the suicide rates were previously very high. Especially the results of complex and sophisticated analyses show that this relationship cannot be explained by potential confounding variables. It can be seen as a very robust finding due to the fact that it could be replicated in several countries under different psychosocial and care conditions. Apparently, in terms of suicide rates certain subgroups of the population are influenced to different degrees by the prescription of antidepressants. However, these findings are not so consistent over different studies. The degree of the suicide prophylactic effect of antidepressants varies among the studies. Isacsson et al. [55], for example, found that the risk for suicide among depressed patients who were treated with antidepressants in Sweden was 141 per 100,000 person years and, among the untreated, 259 per 100,000 person years (i.e. 1.8 times higher among the untreated).

Intervention studies in the context of awareness/education campaigns

The most common psychiatric illness seen as being associated with suicide is a depressive disorder [6]. Although a lot of patients seek professional help in the month before committing suicide [56], post mortem studies show that most patients are untreated at the time of death [57–59]. The huge proportion of underdiagnosed and undertreated depressive patients is also known from several studies on the care of depressive patients, e.g. the DEPRES study [60–63].

An effective prevention strategy for suicidal behaviour must take into account the most consistent results of modern suicide research. Among these are the facts that most individuals who have committed suicide were depressed [64], and that very few of these had received adequate antidepressant treatment [5, 56, 57, 65–67]. This also appears to be true for suicide attempters, including those who later commit suicide [17, 68–70]. According to Isacsson [8] they were thus recruited from that group of depressed individuals in the population who have not received adequate antidepressant treatment [55, 71]. Thus, it seems reasonable, to suggest that a main strategy for lowering suicide rates should be to identify all individuals with depressive disorders and to intervene effectively, which includes antidepressant medication [8, 55, 66].

Awareness and education campaigns seem to be an appropriate approach to achieving this goal [72]. A milestone in this respect is the so-called Gotland study [73]. In 1983–1984 the Swedish Committee for the Prevention and Treatment of Depression offered an educational programme on diagnosis and treatment of depressive disorders to all general practitioners on the island of Gotland. The programme was carefully evaluated; 1982 was used as the baseline and the main evaluation was carried out in 1985. After the educational programmes, the frequency of sick leave for depressive disorders decreased, the frequency of inpatient care for depressive disorders decreased to 30% of that at the baseline; the prescription of antidepressants increased, but prescription of major tranquilizers, sedatives and hypnotics decreased. The frequency of suicide on the island decreased significantly. In 1988, 3 years after the project ended, the inpatient care for depressive disorders increased, the suicidal rate returned almost to baseline values and the prescription of antidepressants stabilized [73]. Thus, the effect of the programme was only observed during the time of the intervention and did not continue after its termination.

As the decrease in suicide rates apparently cannot be attributed to other more general factors, e.g. psychosocial factors, it seems fair to ascribe it to the educational programme. However, it is not easy to detect the most relevant suicide-preventing factor of such a programme. Beside improved health care in terms of diagnosis and treatment of depression, in particular changes in the prescription of psychoactive drugs, particularly antidepressants, have to be considered. In the first control period, the prescription of antidepressants on Gotland was significantly below the frequency in Sweden as a whole. During the years when the educational programme was implemented, the values approached those in Sweden, probably reflecting the fact that the GPs identified more patients with depressive disorders and treated them more accurately. After 1985, the values stabilised and the trend on Gotland became more similar to the trend in the whole of Sweden. However, more depressed patients were identified and treated during the years 1983–1985 and, in the years after, more patients seem to have been identified as candidates for prophylactic treatment, especially with lithium salts. Accordingly, the values for lithium treatment started to rise relative to the trend in Sweden during 1985–1988 [73].

An analysis of temporal associations shows that especially the increase of the prescription rate of antidepressants is related to a decreased suicide rate. The increased rate of lithium prescriptions started too late to explain the decrease of suicide rates. However, it is puzzling that although the prescription rate of antidepressants stabilised at the higher level, the suicide rates increased again one year after the optimal effect of the intervention programme was achieved. In the authors' view another explanation is therefore required for this apparently paradoxical result, for example that at that time antidepressants were no longer restricted to the treatment of depression but started to be prescribed for a broader range of indications, for example the field of anxiety disorders. However, it should be noted that this argumentation is hypothetical.

It is also of interest to examine why the general suicide-preventing effect of the educational programme diminished. The authors see at least two important explanations for these decreasing effects. First, in 1988 only 50% of the GPs who underwent the educational programmes were still working as GPs on Gotland. An increasing number of GPs on Gotland have never been able to attend the educational programmes. The other reason is that people tend to forget, the GPs attend a lot of other educational programmes in other fields, and their interest gradually turns from depressive disorders to other important fields [73].

A programme entitled 'Defeat Depression Campaign' was performed in Great Britain for five years from 1992 to 1996. It was aimed at enhancing public awareness of and attitudes to depressive disorders, providing professional education for general practitioners and reducing the suicide rate [74]. The "Defeat Depression Campaign" was evaluated through three representative surveys of public attitudes (1991, 1995, 1997) [75]. The surveys showed a progressive increase in the general population's knowledge about the biological causes of depressive disorders. However, the campaign did not result in a sustained improvement of patient care [76] or in a change of entrenched public attitudes, for example the negative opinion about treatment with antidepressants [77]. However, a short-term increase of knowledge in the public could be demonstrated. The suicide rate in Great Britain fell over the period 1992–1995 from 11.59 to 10.65, however, due to methodological limitations the influence of the campaign on this indicator remains unclear. The prescription rate of TCAs increased over the course of the campaign from 8,226 (thousands) in 1992 to 9106 (thousands) in 1996, and the prescription rate of SSRIs from 1,178 (thousands) to 5,400 (thousands) [75]. A basic problem of the study is that there was no control region so that it cannot be elucidated whether the measured effects were related to the campaign or possible changes in the health care system.

The 'Nuremberg Alliance Programme', which was performed in the German city of Nuremberg, is another even more complex study which combined an educational programme addressed at general practitioners with a public awareness campaign for depression [78–80]. It was able to confirm the principal results of the Gotland study while using a more sophisticated evaluation methodology, for example involvement of a control region in the evaluation. In the 24 months of the campaign approximately 100 training sessions (for more than 2000 community facilitators) and over 40 public events took place, in close cooperation with local institutions. In order to evaluate the effects of the action programme 'Nuremberg Alliance against Depression', the measured criteria were compared to those in the control region Wurzburg. The primary, prospective outcome criterion was the change in the frequency of suicidal behaviour (suicides and attempted suicides). Data collection commenced in 2000 in Nuremberg. The intervention period was from January 2001 to December 2002. Compared to baseline and the control region there was a significant decrease (24%) of suicidal behaviour. As a secondary outcome criterion, attempted suicide and suicide were evaluated separately; attempted suicides decreased by 26% in Nuremberg. The mean reduction of suicides in Nuremberg was 18%. However, this difference did not differ significantly from the control region and, due to the large annual variations in suicide rates, it was not outside the confidence interval even when the suicide rates in Nuremberg in the previous 12 years were considered [78].

As is always the case in such quasi experimental but complex intervention programmes, it is difficult

to decide which factors are relevant for the achieved effects. Besides the improved diagnosis and treatment of depression, changes in the prescription rate of antidepressants are probably also relevant. As data on changes in the prescription rate of antidepressants are not yet available from the Nuremberg Alliance Programme, no further remarks can be made about this aspect at the moment.

Follow-up studies

Finally, naturalistic follow-up studies will be discussed. The Swiss long-term, follow-up study by Angst et al. [81], which was performed according to a naturalistic design typical for such long-term studies, investigated among others the question as to what extent psychopharmacological treatment influences the suicide rate in patients with mood disorders. Hospitalised patients with affective disorders (n = 406) were followed prospectively for 22 years or more. Later, mortality was assessed for 99% of them, at which time 76% had died. Standardised Mortality Rates (observed deaths/expected deaths) for patients were elevated, especially for suicide and circulatory disorders, in both men and women. Women actually had higher suicide rates but that did not take into account the twofold increase in general population rates for men. Unipolar patients had significantly higher rates of suicide than those with bipolar I or II disorder. In all groups, long-term medication treatment with antidepressants alone or with a neuroleptic, or with lithium in combination with antidepressants and/or neuroleptics, significantly lowered suicide rates even though the treated were more severely ill. These results do not prove directly that the decrease of suicide in patients with long-term medication was strictly caused by the medication itself. Such a conclusion could only be drawn from a well-designed, experimental, prospective trial. But the data are suggestive of a positive drug effect and certainly raise the hypothesis of a positive effect of a long-term medication with antidepressants or of a combination of antidepressants with neuroleptics or lithium. It may be surprising that prescription of antidepressants, even given to bipolar patients, was correlated so strongly with lower suicide rates [81]. This seems interesting in the context of the current critical discussion about the place of antidepressants in the treatment of bipolar depression [82]. Even though data about treatment effects obtained from naturalistic follow-up studies have to be interpreted with the greatest caution (as Angst et al. do), the presented results still have a certain power of persuasion with respect to the suicide-prophylactic effect of antidepressants in the long-term treatment of patients with mood disorders.

In a naturalistic follow-up study published by Yerevanian et al. [83], which was performed in a psychiatric outpatient centre in Los Angeles (USA), the rates of suicidal behaviour during versus after discontinuation of treatment with antidepressants were compared in patients with unipolar depression. In this study also comparative rates of suicidal behaviour for patients maintained on tricyclic antidepressants versus SSRIs were investigated. Charts were reviewed for 521 patients with major depressive disorder and/or dysthymic disorder and periods of active treatment or discontinuation with SSRIs or TCAs were determined. Rates of completed suicide, suicide attempts and hospitalization for suicidality were analysed. There was a greater than five-fold increase in risk for suicidal behaviour after discontinuation of antidepressant treatment ($P < 0.0001$). The rates of suicidal behaviour during treatment with SSRIs or TCAs were similar. The principle finding of this study was that discontinuation of antidepressants, irrespective of the class to which they belong, is associated with high risks. The fact that after discontinuation of antidepressants the rates of suicidal behaviour rose suggests that antidepressant treatment may have had a protective effect against suicidal behaviour. This interpretation must be made with caution, as in this study all 'OFF' medication periods were *after* discontinuation and 'not OFF' periods *prior* to treatment. The apparent heightened risk period following discontinuation could be due to several factors, including: (1) discontinuation-associated re-emergence of clinical depression; (2) a pharmacologic rebound effect of worsening suicidality; (3) a physiological discontinuation syndrome and (4) hopelessness, leading to treatment discontinuation [83].

Taken together, the study results presented above give some further hints that treatment of depressive patients with antidepressants can obviously reduce the risk of suicidal behaviour.

Summary

The effect of antidepressants on suicidality is difficult to investigate in randomised, controlled studies due to several methodological limitations. This is true for both aspects, i.e. decrease or increase of suicidality. A broad scientific approach therefore uses complementary methods and considers randomised, controlled clinical studies, different kinds of epidemiological studies, quasi-experimental intervention studies, naturalistic follow-up studies, etc. to obtain the most comprehensive evidence.

Suicidality should be differentiated into at least three subcategories: suicidal thoughts, suicide attempts and completed suicide. As is known from research in suicidology, these subcategories are only partially related and should therefore be differentiated from one another.

Altogether, the findings of randomised, control group studies in acute depressive patients supply some evidence that antidepressants are able to reduce

suicidal thoughts in depressive patients. This effect is associated with the global antidepressive effect. However, when comparing different antidepressants it appears that, although they show the same global antidepressive efficacy, there might be differences in their speed or capacity to reduce suicidal thoughts. This point was a particular focus of discussion for the SSRIs, but the hypothesis that SSRIs have a faster/stronger effect on the reduction of suicidal thoughts could not be confirmed when the results of all randomised, control group studies were viewed collectively, although some studies point in this direction.

However, data from randomised control group studies in acute depressive patients give no support to the hypothesis that antidepressants can reduce suicide attempts or suicide. The extremely low basal rate of suicidal behaviour in these studies is apparently a principal methodological problem which makes it almost impossible to demonstrate under such conditions a beneficial effect of antidepressants on suicidal behaviour. Even meta-analyses of huge data sets from randomised controlled trials seem unable to overcome this problem. Thus, complementary methodological approaches have to be applied.

When considering the results of epidemiological studies, it becomes evident that increased utilisation of antidepressants is accompanied by a relevant decline of national suicide rates in several countries, particularly in those where the suicide rates were previously very high. According to the results of complex and sophisticated analyses this relationship cannot be explained by potential confounding variables. This can be seen as a very robust finding due to the fact that it could be replicated in several countries under different psychosocial and care conditions. Apparently, in terms of suicide rates, certain subgroups of the population are influenced to different degrees by the prescription of antidepressants. However, these findings are not so consistent over different studies.

Additional supportive data come from awareness/education campaigns with a quasi-experimental design, as well as from follow-up studies. However, especially the latter have to be interpreted with caution due to the naturalistic design.

Altogether, there seems to be reasonable evidence from different research approaches that antidepressants are able to reduce suicidal ideation and also suicide in depressive patients. While the evidence for the beneficial effect on suicidal ideation comes from randomised, control group studies, some of which used a placebo arm, the evidence for the prophylactic effect on suicide was primarily obtained from well-designed epidemiological studies. As to suicide attempts, the date are not robust enough to draw clear conclusions.

Going beyond the scope of this review, the important role of another drug, lithium, in the field of suicide prevention should be mentioned briefly. Several analyses of lithium prevention studies show that the excess mortality usually shown by depressive patients in comparison to the general population can be reduced to the normal level by lithium relapse prophylaxis. This effect of lithium could not only be explained by its relapse-prophylactic effect but was interpreted as being a specific influence on suicidality, potentially by the serotonergic effects of lithium [84–88]. The finding that a raised lithium concentration in drinking water correlates with a lower suicide rate is also of interest [89].

Finally, it should be stated that suicide prevention is a very complex issue and beside psychopharmacological interventions, also requires the involvement of different kinds of psychosocial strategies to obtain the goal of maximum efficacy [72].

The question whether antidepressants can induce or aggravate suicidal ideation, or even stimulate suicidal behaviour, was not addressed in this paper. This issue will be covered in another review [13].

References

1. Bradvik L (2002) The occurrence of suicide in severe depression related to the months of the year and the days of the week. Eur Arch Psychiatry Clin Neurosci 252:28–32
2. Bradvik L, Berglund M (2000) Suidical ideation in severe depression. Eur Arch Psychiatry Clin Neurosci 250:139–143
3. Bradvik L, Berglund M (2004) Suicide in severe depression related to treatment: depressive characteristics and rate of antidepressant overdose. Eur Arch Psychiatry Clin Neurosci 255:245–250
4. Gibbons RD, Hur K, Bhaumik DK, Mann JJ (2005) The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 62:165–172
5. Isometsa ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI, Lonnqvist JK (1994) Suicide in major depression. Am J Psychiatry 151:530–536
6. Moller HJ (2003) Suicide, suicidality and suicide prevention in affective disorders. Acta Psychiatr Scand 108(Suppl. 418):73–80
7. Baldwin D, Bullock T, Montgomery D, Montgomery S (1991) 5-HT reuptake inhibitors, tricyclic antidepressants and suicidal behaviour. Int Clin Psychopharmacol 6(Suppl. 3):49–55
8. Isacsson G (2000) Suicide prevention–a medical breakthrough? Acta Psychiatr Scand 102:113–117
9. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B (2005) Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 330:396
10. Möller HJ (1992) Antidepressants – do they decrease or increase suicidality? Pharmacopsychiatry 25:249–253
11. Teicher MH, Glod CA, Cole JO (1993) Antidepressant drugs and the emergence of suicidal tendencies. Drug Saf 8:186–212
12. Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ (2004) Antidepressants and suicide risk in the United States, 1985–1999. J Clin Psychiatry 65:1456–1462
13. Möller HJ (2006) Is there evidence for negative effects of antidepressants on suicidality in depressive patients? Eur Arch Psychiatry Clin Neurosci In Press
14. Kurz A, Möller HJ, Baindl G, Burk F, Torhorst A, Wachtler C, Lauter H (1987) Classification of parasuicide by cluster analysis. Types of suicidal behaviour, therapeutic and prognostic implications. Br J Psychiatry 150:520–525

15. Kurz A, Möller HJ, Torhorst A, Lauter H (1988) Validation of six risk scales for suicide attempters. In: Möller HJ, Schmidtke A, Welz R (eds) Current issues of suicidology. Springer, Berlin, Heidelberg, New York, pp 174–178
16. Lejoyeux M, Leon E, Rouillon F (1994) Prevalence and risk factors of suicide and attempted suicide. Encephale 20:495–503
17. Möller HJ (1990) Suicide risk and treatment problems in patients who have attempted suicide. In: Lester D (eds) Current concepts of suicide. Charles Press, Philadelphia, pp 168–181
18. Brown GK, Beck AT, Steer RA, Grisham JR (2000) Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. J Consult Clin Psychol 68:371–377
19. Moscicki EK (1999) Epidemiology of suicide. In: Jacobs D (eds) The Harvard Medical School guide to suicide assessment and intervention. Jossey-Bass, San Francisco, pp 40–51
20. ACNP (1993) Suicidal behavior and psychotropic medication. Accepted as a consensus statement by the ACNP Council, March 2, 1992. Neuropsychopharmacology 8:177–183
21. Montgomery S, Cronholm B, Asberg M, Montgomery DB (1978) Differential effects on suicidal ideation of mianserin, maprotiline and amitriptyline. Br J Clin Pharmacol 5 (Suppl. 1):77S–80S
22. Asberg M, Nordström P (1988) Biological correlates of suicidal behaviour. In: Möller HJ, Schmidtke A, Welz R (eds) Current issues of suicidology. Springer, Berlin, Heidelberg, New York, pp 221–241
23. Traskman L, Asberg M, Bertilsson L, Sjostrand L (1981) Monoamine metabolites in CSF and suicidal behavior. Arch Gen Psychiatry 38:631–636
24. Rujescu D, Giegling I, Sato T, Möller HJ (2001) A polymorphism in the promoter of the serotonin transporter gene is not associated with suicidal behavior. Psychiatric Genet 11:169–172
25. Rujescu D, Giegling I, Sato T, Hartmann AM, Moller HJ (2003) Genetic variations in tryptophan hydroxylase in suicidal behavior: analysis and meta-analysis. Biol Psychiatry 54:465–473
26. Rujescu D, Giegling I, Sato T, Moller HJ (2003) Lack of association between serotonin 5-HT1B receptor gene polymorphism and suicidal behavior. Am J Med Genet 116B:69–71
27. Montgomery SA, McAuley R, Rani SJ, Roy D, Montgomery DB (1981) A double blind comparison of zimelidine and amitriptyline in endogenous depression. Acta Psychiatr Scand Suppl 290:314–327
28. de Wilde J, Mertens C, Overo KF, Petersen HE (1985) Citalopram versus mianserin. A controlled, double-blind trial in depressed patients. Acta Psychiatr Scand 72:89–96
29. Spitzer RL, Endicott J, Robins E (1978) Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 35:773–782
30. Amin MM, Anath JV, Coleman BS, Darcourt G, Farkas T, Goldstein BJ, Lapierre YD, Paykel ES, Wakelin JS (1984) Fluvoxamine antidepressant effects confirmed in a placebo-controlled international study. Clin Neuropharmacol 7(Suppl. 1):580–581
31. Wakelin JS (1988) The role of serotonin in depression and suicide: do serotonin reuptake inhibitors provide a key? In: Mendlewitcz JH, van Praag M (eds) Advances in biological psychiatry. Karger, Basel, pp 70–80
32. Muijen M, Roy D, Silverstone T, Mehmet A, Christie M (1988) A comparative clinical trial of fluoxetine, mianserin and placebo in depressed outpatients. Acta Psychiatr Scand 78:384–390
33. Möller HJ, Steinmeyer EM (1994) Are serotonergic reuptake inhibitors more potent in reducing suicidality? An empirical study on paroxetine. Eur Neuropsychopharmacol 4:55–59
34. Beasley CM Jr., Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH Jr., Heiligenstein JH, Thompson VL, Murphy DJ, Masica DN (1991) Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 303:685–692
35. Montgomery SA (1992) The advantages of paroxetine in different subgroups of depression. Int Clin Psychopharmacol 6(Suppl. 4):91–100
36. Lopez-Ibor JJ (1993) Reduced suicidality with paroxetine. Eur Psychiatry 8(Suppl. 1):17s–19s
37. Pedersen AG (2005) Escitalopram and suicidality in adult depression and anxiety. Int Clin Psychopharmacol 20:139–143
38. Khan A, Warner HA, Brown WA (2000) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry 57:311–317
39. Khan A, Khan SR, Leventhal RM, Brown WA (2001) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database. Int J Neuropsychopharmacol 4:113–118
40. Khan A, Khan S, Kolts R, Brown WA (2003) Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 160:790–792
41. Storosum JG, van Zwieten BJ, van den BW, Gersons BP, Broekmans AW (2001) Suicide risk in placebo-controlled studies of major depression. Am J Psychiatry 158:1271–1275
42. Gunnell D, Saperia J, Ashby D (2005) Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 330:385
43. Carlsten A, Waern M, Ekedahl A, Ranstam J (2001) Antidepressant medication and suicide in Sweden. Pharmacoepidemiol Drug Saf 10:525–530
44. Rihmer Z (2001) Can better recognition and treatment of depression reduce suicide rates? A brief review. Eur Psychiatry 16:406–409
45. Rihmer Z, Appleby L, Rihmer A, Belso N (2000) Decreasing suicide in Hungary. Br J Psychiatry 177:84
46. Rihmer Z, Rutz W, Pihlgren H, Pestality P (1998) Decreasing tendency of seasonality in suicide may indicate lowering rate of depressive suicides in the population. Psychiatry Res 81:233–240
47. Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P (2003) Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. BMJ 326:1008
48. Olfson M, Shaffer D, Marcus SC, Greenberg T (2003) Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 60:978–982
49. FDA Public Health Advisory (2004) Suicidality in children and adolescents being treated with antidepressant medications. www. fda. gov/cder/drug/antidepressants/SSRIPHA200410
50. Kelly CB, Ansari T, Rafferty T, Stevenson M (2003) Antidepressant prescribing and suicide rate in Northern Ireland. Eur Psychiatry 18:325–328
51. Barbui C, Campomori A, D'Avanzo B, Negri E, Garattini S (1999) Antidepressant drug use in Italy since the introduction of SSRIs: national trends, regional differences and impact on suicide rates. Soc Psychiatry Psychiatr Epidemiol 34:152–156
52. Helgason T, Tomasson H, Zoega T (2004) Antidepressants and public health in Iceland. Time series analysis of national data. Br J Psychiatry 184:157–162
53. Rihmer Z (2004) Decreasing national suicide rates–fact or fiction? World J Biol Psychiatry 5:55–56
54. Van Praag HM (2003) A stubborn behaviour: the failure of antidepressants to reduce suicide rates. World J Biol Psychiatry 4:184–191

54a. Rihmer Z, Belso N, Kalmar S (2001) Antidepressants and suicide prevention in Hungery. Acta Psychiatr Scand 103:238–239

55. Isacsson G, Bergman U, Rich CL (1996) Epidemiological data suggest antidepressants reduce suicide risk among depressives. J Affect Disord 41:1–8
56. Isacsson G, Boethius G, Bergman U (1992) Low level of antidepressant prescription for people who later commit suicide: 15 years of experience from a population-based drug database in Sweden. Acta Psychiatr Scand 85:444–448
57. Isacsson G, Holmgren P, Druid H, Bergman U (1997) The utilization of antidepressants – a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992–1994. Acta Psychiatr Scand 96:94–100
58. Isometsa E, Henriksson M, Heikkinen M, Aro H, Lonnqvist J (1994) Suicide and the use of antidepressants. Drug treatment of depression is inadequate. BMJ 308:915

59. Oquendo MA, Malone KM, Ellis SP, Sackeim HA, Mann JJ (1999) Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 156:190–194
60. Angst J, Gamma A, Gastpar M, Lepine JP, Mendlewicz J, Tylee A (2002) Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. Eur Arch Psychiatry Clin Neurosci 252:201–209
61. Lepine JP, Gastpar M, Mendlewicz J, Tylee A (1997) Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol 12:19–29
62. Tylee A, Gastpar M, Lepine JP, Mendlewicz J (1999) DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. DEPRES Steering Committee. Int Clin Psychopharmacol 14:139–151
63. Tylee A, Gastpar M, Lepine JP, Mendlewicz J (1999) Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) survey. DEPRES Steering Committee. Int Clin Psychopharmacol 14:153–165
64. Cheng AT (1995) Mental illness and suicide. A case–control study in east Taiwan. Arch Gen Psychiatry 52:594–603
65. Isacsson G, Bergman U, Rich CL (1994) Antidepressants, depression and suicide: an analysis of the San Diego study. J Affect Disord 32:277–286
66. Isacsson G, Holmgren P, Wasserman D, Bergman U (1994) Use of antidepressants among people committing suicide in Sweden. BMJ 308:506–509
67. Rich CL, Isacsson G (1997) Suicide and antidepressants in south Alabama: evidence for improved treatment of depression. J Affect Disord 45:135–142
68. Isacsson G, Wasserman D, Bergman U (1995) Self-poisonings with antidepressants and other psychotropics in an urban area of Sweden. Ann Clin Psychiatry 7:113–118
69. Kurz A, Möller HJ, Burk F, Torhorst A, Wachtler C, Lauter H (1985) Determination of treatment disposal for parasuicide patients in a German university hospital. Soc Psychiatry 20:145–151
70. Wasserman D, Persson ML (1993) Suicide. Lancet 342:745
71. Priest RG (1994) Improving the management and knowledge of depression. Br J Psychiatry 164:285–287
72. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lonnqvist J, Malone K, Marusic A, et al. (2005) Suicide prevention strategies: a systematic review. JAMA 294:2064–2074
73. Rutz W, von Knorring L, Walinder J (1992) Long-term effects of an educational program for general practitioners given by the Swedish Committee for the Prevention and Treatment of Depression. Acta Psychiatr Scand 85:83–88
74. Paykel ES, Tylee A, Wright A, Priest RG, Rix S, Hart D (1997) The Defeat Depression Campaign: psychiatry in the public arena. Am J Psychiatry 154:59–65
75. Paykel ES (2001) Impact of public and general practice education in depression: evaluation of the defeat depression campaign. Psychiatria Fennica 32(Suppl. 2):51–61
76. Rix S, Paykel ES, Lelliott P, Tylee A, Freeling P, Gask L, Hart D (1999) Impact of a national campaign on GP education: an evaluation of the Defeat Depression Campaign. Br J Gen Pract 49:99–102
77. Paykel ES, Hart D, Priest RG (1998) Changes in public attitudes to depression during the Defeat Depression Campaign. Br J Psychiatry 173:519–522
78. Althaus D, Niklewski G, Pfeiffer-Gerschel T, Schmidtke A, Hegerl U (2005) Vom "Nürnberger Bündnis gegen Depression" zur "European Alliance against Depression". Modelle zur Optimierung der Versorgung depressiver Patienten. Nervenheilkunde 24:402–407
79. Hegerl U, Althaus D, Stefanek J (2003) Public attitudes towards treatment of depression: effects of an information campaign. Pharmacopsychiatry 36:288–291
80. Henkel V, Mergl R, Kohnen R, Maier W, Moller HJ, Hegerl U (2003) Identifying depression in primary care: a comparison of different methods in a prospective cohort study. BMJ 326:200–201
81. Angst F, Stassen HH, Clayton PJ, Angst J (2002) Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 68:167–181
82. Moller HJ, Grunze H, Broich K (2006) Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants are the treatment of choice? A conceptual review. Eur Arch Psychiatry Clin Neurosci 256:1–16
83. Yerevanian BI, Koek RJ, Feusner JD, Hwang S, Mintz J (2004) Antidepressants and suicidal behaviour in unipolar depression. Acta Psychiatr Scand 110:452–458
84. Cipriani A, Pretty H, Hawton K, Geddes JR (2005) Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 162:1805–1819
85. Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C (1991) Does lithium reduce the mortality of recurrent mood disorders? J Affect Disord 23:1–7
86. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D (2003) Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 290:1467–1473
87. Müller-Oerlinghausen B (1989) Pharmakotherapie pathologischen aggressiven und autoaggressiven Verhaltens. In: Pöldinger W, Wagner W (eds) Aggression, Selbstaggression, Familie und Gesellschaft. Springer, Berlin, Heidelberg, New York, pp 121–134
88. Tondo L, Hennen J, Baldessarini RJ (2001) Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. Acta Psychiatr Scand 104:163–172
89. Schrauzer GN, Shrestha KP (1990) Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elem Res 25:105–113