PSYCHOPHARMACOLOGICAL TREATMENT OF SUICIDAL IDEATION AND BEHAVIOUR IN THE FRAME OF MENTAL DISORDERS

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Abstract

This paper is a narrative review describing the place of antidepressants and other psychoactive medications in the treatment of suicidal ideation and behaviour associated with psychiatric disorders. Based on evidence as well as clinical experience, antidepressants have a prominent place in this indication, not only in depression but also in depressive syndromes in the context of other psychiatric disorders. The evidence for this is based on relatively few RCTs on the one side and on pharmacoepidemiological studies on the other side. Also anxiolytics and hypnotics are indicated, depending on the respective syndrome and disorder. However, for the latter medications the evidence in the sense of RCTs focussing on suicidality is widely missing. Of interest are data indicating that in schizophrenia, olanzapine might have a better suicidality preventive effect than other antipsychotics. Among the mood stabilizers there are hints from long-term studies predominantly in bipolar depression that lithium might prevent suicide.

Altogether it has to be stated that the whole field needs more systematic research to increase the evidence base. Currently, it is to a large degree more dependent on clinical experience than on evidence.

Key Words: suicidality, antidepressants, psychopharmacology

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1. Introduction

Besides counselling and other psychotherapeutic approaches, psychopharmacological treatment and other biological treatment procedures – e.g. electroconvulsive therapy – are indicated for many suicidal patients. In people at risk of committing suicide, these interventions are usually aimed at actual prevention of suicide, mostly through sedative-anxiolytic or sleep inducing approaches, or at specific treatment of psychiatric disorders that are the underlying cause of suicidality. It is of great importance for patients in a critical situation of their life to be able to disburden themselves of anxieties, depression, agitation, sleeplessness and other disturbing symptoms, even if these are not part of a full syndrome of a psychiatric disorder but only subsyndromal.

The most widely used in the psychopharmacological treatment of predominantly depressive patients with suicidality are naturally antidepressants. Considering this it is astonishing that the evidence base for anti-suicidal efficacy of antidepressants from randomised controlled group studies is relatively small on the one hand, and that on the other hand there was intensive discussion in recent years that antidepressants might have negative effects on suicidality under certain conditions. Due to this situation, the evidence for the beneficial and potentially harmful effects of antidepressants on suicidality, involving all kinds of evidence will be described in the first part of this paper. The second part will focus on the most relevant psychiatric disorders which are often associated with suicidality and where, regarding the psychopharmacological treatment, this aspect has to be considered especially. Depending on the respective disorders this second part goes beyond the spectrum of antidepressants, discussing amongst others also the place of benzodiazepines.

2. Evidence for beneficial effects of antidepressants on suicidality in depressive patients

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 usually also diminish or disappear. However, in the early publications on antidepressants

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there are hardly any special studies on this topic. Much more interest in exploring this matter was shown later in the context of the question whether certain antidepressants reduce suicidal thoughts more quickly or effectively, particularly after the advent of the SSRIs. The evidence and the involved methodological issues were summarised in systematic narrative reviews focussing on the beneficial and possibly harmful effects of antidepressants on suicidality (Möller 2006a, 2006b; Möller et al. 2008). The following argumentation is based on these comprehensive reviews.

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 that suicidal ideation improved significantly more with fluoxetine than with placebo (72.0% vs 54.8%, $p<0.001$) and was similar to the improvement with TCAs (72.5% vs 69.8%, $p=0.294$) (Beasley Jr. et al. 1991). It is important to underline that in terms of suicidal behaviour (suicide attempts and suicide) there is no significant difference: the pooled incidence of suicidal acts was 0.3% for fluoxetine, 0.2% for placebo and 0.4% for tricyclics. 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% (Beasley Jr. et al. 1991). Similar results were also obtained in the pooled analysis of the results of a paroxetine study (Lopez-Ibor 1993). 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 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 paroxetine, 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.

Altogether, these findings provide some evidence that antidepressants are able to reduce suicidal thoughts in depressive patients. This effect is associated with the global antidepressive effect (Möller 2006a).

From a clinical perspective one might hypothesise 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 adequately. The 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 data sets involving not only one experimental antidepressant but several are apparently not able to overcome the respective power problem of individual studies. Khan et al. (Khan et al. 2000, 2001, 2003) analysed several FDA databases on randomised, placebo- and/or active comparator-controlled trials on new antidepressants, mostly SSRIs. The analysis of this database did not find any significant differences between placebo, active comparator or investigational antidepressants in the rates of attempted or completed suicide. A similar meta-analysis (Storosum et al. 2001) where all randomised and placebo-controlled, double-blind, short- and long-term studies of an antidepressant that were part of a registration dossier submitted to the Dutch regulatory authority between 1983 and 1997 were reviewed for attempted suicide, came to a similar result. In contrast, two other meta-analyses (Fergusson et al. 2005, Gunnell et al. 2005) found an increased risk of suicide attempts for antidepressants, whereby in the latter study the risk was only small and did not reach statistical significance.

Thus, the overall findings from pooled analyses/meta-analyses of results of randomised, controlled, short- and long-term trials (mostly up to one year) do not support the hypothesis that antidepressants reduce attempted or completed suicide (Möller 2006a). The result of the meta-analysis by Fergusson et al. (Fergusson et al. 2005) that, in contrast to the general expectations, there might be an increased risk of suicidal behaviour as a consequence of treatment with antidepressants, will be further discussed in the next chapter (Möller 2006b).

Interesting data demonstrating the effectiveness of antidepressants to reduce suicidal behaviour were obtained in recent years from pharmacoepidemiological studies (Möller 2006a). In view of the fact that it appears to be difficult to prove the anti-suicidal effect of antidepressants in randomised, control group studies, such a naturalistic approach seems to be one of the best ways to obtain at least some evidence. These studies are backed up by data from awareness and follow-up trials. However, naturalistic studies are always difficult to interpret due to several potential confounding factors which require careful consideration. The prescription rate of antidepressants has increased in several countries in the past decades, 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 lower and higher prescription rate can be compared. For example, Isacsson analysed such data in a study on suicide rates in Sweden and other Scandinavian countries (Isacsson 2000). He took into account relevant confounding factors which might explain the change in suicide rates, like unemployment rates and alcohol consumption. 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 ($rho = -0.90$, $p<0.05$). 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 1990-96. Testing potential confounders, there was no consistent correlation in Sweden, 1978-96, between suicide rates and alcohol consumption, or between suicide rates and unemployment rates (Isacsson, 2000). In this epidemiological study it appears that the increased use of antidepressants was one of the contributing factors to the decrease in the suicide rate.

This result was supported by the study from

Grunebaum et al. (Grunebaum et al. 2004) on US-American data for the years 1985 to 1999. From 1985 to 1999, the suicide rate fell 13.5%, with a greater decline among women, and antidepressant prescription rates increased over 4-fold, 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. A similar study on suicide data from the USA performed by Gibbons et al. (Gibbons et al. 2005) obtained similar but somewhat more differentiated results. Other epidemiological studies confirmed the positive results (Barak and Aizenberg 2006, Bramness et al. 2007, Hall et al. 2003, Kapusta et al. 2009, Kelly et al. 2003, Milane et al. 2006, Morgan et al. 2004, Nakagawa et al. 2007, Reseland et al. 2006, Rihmer 2001, Rihmer 2004, Sebestyen et al. 2010). In order to give a balanced overview it should be mentioned that some studies were unable to support the findings of an association between an increased prescription rate of antidepressants and a decreased suicide rate (Barbui et al. 1999, Helgason et al. 2004, Guaiana et al. 2005).

These studies on an epidemiological level show that it is evident that an increased utilisation of antidepressants, especially SSRIs, was accompanied by a relevant decline of national suicide rates in several countries (Möller 2006a), particularly in those where the suicide rates were previously very high. 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 the various studies. The degree of the suicide prophylactic effect of antidepressants varies among the studies. Isacsson et al. (Isacsson et al. 1996), 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).

The most common psychiatric illness seen to be associated with suicide is a depressive disorder (Möller 2003). Although a lot of patients seek professional help in the month before committing suicide (Isacsson et al., 1992), post mortem studies show that most patients are untreated at the time of death (Isacsson et al. 1997, Oquendo et al. 1999, Isometsa et al. 1994). 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 (Angst et al. 2002; Tylee et al. 1999b, 1999a; Lepine et al. 1997). Thus, it seems reasonable to suggest that the important strategy for lowering suicide rates should be to identify all individuals with depressive disorders and to intervene effectively. Awareness and education campaigns seem to be an appropriate approach to achieving this goal (Mann et al. 2005). Several quasi experimental complex intervention programmes of this kind were performed with positive results. It is difficult to decide which factors are responsible for the achieved effects. Besides the improved diagnosis and treatment of depression, changes in the prescription rate of antidepressants are probably also relevant (Paykel et al. 1998, Rutz et al. 1992, Hegerl et al. 2008, Pfeiffer-Gerschel 2007).

Together with additional naturalistic data from cohort studies 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 (Möller 2006a).

3. Can antidepressants increase suicidal ideation or the risk of suicidal behaviour?

The question whether antidepressants can induce or aggravate suicidal ideation, or even stimulate suicidal behaviour, should be briefly addressed in this paper because it has attracted so much attention in the past years, especially in the field of child and adolescent psychiatry. A comprehensive review (Möller 2006b) and the WPA section on pharmacopsychiatry (Tandon et al. 2008) all raised this issue in detail. Therefore, only a short summary will be presented here which came to the following results in this respect:

Randomised, controlled studies do not supply much evidence to support the hypothesis that antidepressants in general or individual antidepressants have suicidality-inducing effects. Several meta-analyses comparing datasets of individual antidepressants, mostly SSRIs, demonstrated that the categories 'worsening of pre-existing suicidal thoughts' or 'new emergence of suicidal thoughts' were less frequent in the SSRI or TCA groups than in the placebo groups. Meta-analyses on datasets of novel antidepressants from national drug authorities which took the suicide attempt rate or suicide rate as the outcome criterion often failed to demonstrate a suicidality-increasing effect of antidepressants. However, there are signals for suicidality inducing effects, coming from metaanalyses of the most comprehensive data sets. The meta-analysis by Fergusson et al. (Fergusson et al. 2005) found an increased risk of suicide attempts for SSRIs compared to placebo, but not different from TCAs. The meta-analysis by Gunnell (Gunnell et al. 2005) supported this but with a weaker level of evidence. A meta-analysis by the FDA of the antidepressant studies in children or adolescents found an increase of suicidal thoughts and behaviour but not suicide (FDA Public Health Advisory 2004; Hammad 2004; Hammad et al. 2006a, 2006b) which does not appear to be specific to the SSRIs.

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 (Stone et al. 2009). This meta-analysis included the most comprehensive database of placebo-controlled trials for various indications in this

research field. 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% Cl, 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. Apparently, age effects play an important modulating role. 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, whereafter the risk is even reduced. Since suicidal behaviour is probably more meaningfully related to suicide risk in older age groups, these findings are moderately reassuring.

Pharmacoepidemiological studies which search for associations between prescription rates of antidepressants and the risk of suicide attempts (not suicide) in clinical cohorts on an individual level are not fully conclusive (Möller 2006b).

Related to this problem is the issue of differences in the fatal toxicity of antidepressants. There is clear evidence that most modern antidepressants like the SSRIs have a lower fatal toxicity risk than the TCAs (Möller 2006b).

Even though statistical analyses of control group studies or epidemiological data about available psychopharmaceutical agents may not deliver strong indications for a suicidality-inducing effect of SSRIs or antidepressants in general but possibly only in subgroups, the principle possibility of such an adverse effect in single cases should always be considered carefully. Especially children, adolescents and younger adults as well as in the face of the frequently very complex clinical situation that is characterised by non-response, co-medication, comorbidity, personality factors and situational stress, among others (Stübner et al. 2010).

In everyday clinical practice the discussion about the possible risks of SSRIs or antidepressants in general should not result in clinicians forgetting the benefits of these drugs. The symptoms of depression require an effective drug treatment accompanied by the chance to reduce suicidal thoughts. Of course, particularly at the start of treatment patients are often very labile and in single cases antidepressants, probably depending on their specific pharmacological and pharmacodynamic characteristics and in interaction with special characteristics of the patient such as personality traits, comorbidity etc., can induce or enhance suicidal thoughts or even reduce the threshold level for suicide attempts. It is a question of good clinical practice to monitor the patient carefully, especially at the start of a drug treatment, and to try to avoid any kind of risk. If agitation, sleep disturbances or other drug side effects that may potentially induce or enhance suicidality occur, a sedating or sleep-inducing co-medication should be administered. It is also of greatest importance to offer the patient a substantial supportive psychotherapy. Finally, it should not be forgotten that depressive symptoms and suicidal thoughts can fluctuate during the day or over longer time periods. It is often difficult to follow this carefully enough on an outpatient basis, so that inpatient treatment might be a better option for patients at risk. It has been demonstrated that the use of antidepressants under the conditions of good clinical practice is effective and safe considering the different phenomena of suicidality (Seemüller et al. 2009).

4. Psychopharmacological treatment of suicidality in the context of psychiatric disorders

Unipolar and bipolar depression

Depression is seen as the most frequent cause of suicidality and suicide. Although the suicide lifetime risk in depressed patients is not much higher than for example in schizophrenic patients, depression is the most frequent reason for suicidality and suicide due to the high prevalence rate of depression. Suicidal ideation and behaviour in depression is state and severity dependent (Rihmer 2007). As to the differentiation between unipolar and bipolar depression, the suicide risk rate is more or less the same, i.e. about 10 – 15 % lifetime risk. Suicidal thoughts occur almost regularly in depression, especially in moderate or severe cases. Furthermore, a large number of patients think about suicidal acts, perform a suicide attempt or even die from suicide. Antidepressants are the treatment of choice to reduce depressive symptoms of the depressive episode (Bauer et al. 2002, 2007) and also suicidal thoughts occurring in this context (Möller 2006a).

When selecting an antidepressant for severely suicidal depressive patients, in some countries traditionally compounds with a sedative profile were favoured (e.g. amitriptyline or doxepin as representatives for the classic tricycles or mitrazepine as an example for a modern antidepressant (Baghai et al. 2006, Möller and Volz 1996), although this view is not accepted as sufficient by evidence based data from an international perspective. Drugs that increase drive, such as MAO inhibitors or desipramine, may increase the risk of suicide and should therefore be avoided (Möller 1992). Another aspect of drug selection is that the antidepressant should be safe in overdose, which is proven for most modern antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs). If a TCA is chosen, the smallest package should be prescribed to avoid the risk of lethal intoxication in case of suicidal overdose. Most TCAs have a high risk of fatal outcome if dosages of 1000 mg or more are taken. SSRIs are nowadays seen as the first-line treatment of depression, particularly under outpatient conditions, and especially with respect to tolerability and compliance (Möller 1992, Möller and Volz 1996). It should be remembered that SSRIs as well as the selective serotonin-noradrenalin reuptake inhibitors (Baghai et al. 2006) have no sedative potential and in some cases even cause agitation.

Agitated depressive patients with suicidal ideations might profit more from a sedative tricyclic

antidepressant or a sedative modern antidepressant like mitrazepine. The degree of sedation achieved by a sedative antidepressant in highly agitated suicidal depressive patients is sometimes insufficient, so that it may be necessary to prescribe a benzodiazepine or a sedative neuroleptic (Möller 1999). The dose depends on the patient's condition and individual reaction. It should be chosen so that the inner restlessness and agitation wear off completely or as far as possible and significant sedation and promotion of nocturnal sleep are achieved. Of course, benzodiazepines should only be described for a minimal period of time to reduce the risk of dependency as much as possible.

In the case of delusional depressions, the administration of potent neuroleptics is indicated as co-medication to the antidepressant treatment. In cases of severe depression with extreme suicidality, electroconvulsive therapy (Bradvik and Berglund 2000, Fink 2005, Isometsa et al. 1996) should be considered because of its rapid onset of action in comparison with antidepressants. Electroconvulsive therapy is also an important option in patients who are refractory to antidepressant treatment (Möller 1994a).

Attention should be paid to two additional problem points when antidepressants are given to suicidal depressive patients. First, immediate antidepressant therapy is contra-indicated in cases of intoxication with psychotropic substances (e.g. in an attempted suicide). In case of need, the fading period of intoxication should be bridged with sedating neuroleptics. Secondly, an increase in drive or normalisation of reduced drive often occurs during antidepressant treatment prior to brightening of mood (so-called drive-mood dissociation). This may require temporary prescription or dose increase of a concomitant sedative medication until mood starts to brighten, in order to counteract the increased risk of acting on suicide impulses. This is of special importance with certain drugs, like the SSRIs, which are not sedative and sometimes even induce agitation or Akathisia (Möller 1992, 2006b). As a general rule, it should be considered that depressive patients treated with antidepressants should be observed carefully in the first days/weeks after treatment indication to assess and counteract as soon as possible negative changes in their degree of suicidality.

Unipolar and bipolar depressions are usually recurrent. Thus, in patients who have had two or more recurrent episodes, treatment is required to prevent relapse subsequent to acute and maintenance treatment. Antidepressants or lithium are candidates for preventing relapse in unipolar depression (Bauer et al. 2002, 2007). In bipolar depression (Grunze et al. 2010b, 2010a), beside lithium carbamazepine, valproate and lamotrigine are the alternatives. More and more atypical antipsychotics have demonstrated relapse/recurrence preventive properties. Of great interest is the increasingly confirmed result that prophylactic treatment with lithium reduces the well-known excess mortality of patients with unipolar or bipolar depression to within the normal range. This effect is apparently not only due to the reduction of depressive relapses and related suicidal behaviour but also seems to be the consequence of a direct effect on suicidal behaviour itself (Thies-Flechtner et al. 1996, Müller-Oerlinghausen and Berghofer 1999, Goodwin et al. 2003, Fleischhacker et al. 2005, Baldessarini et al. 2006). It is not finally answered whether anticonvulsants used as mood stabilizers have a similar potential (Yerevanian et al. 2007a).

Cipriani and co-workers' review and meta-analysis (Cipriani et al. 2005) of 32 randomised trials of lithium versus other compounds (active or placebo) showed that lithium reduced the suicide mortality with approximately 60% and the risk of suicide and deliberate self-harm combined by about 70%. Lithium prophylaxis should therefore clearly be considered for patients with affective disorders who have showed suicidal behaviour.

In the past, no differentiation was made with respect to the drug treatment of depressive episodes occurring during unipolar or bipolar affective disorder. Since last decade, great emphasis was placed on underlining that the treatment of bipolar depression should consider some special issues, especially the risk that antidepressants, mainly the tricyclic antidepressants, may induce a switch into mania. Therefore, some guidelines recommended avoiding antidepressants and favour a monotherapy with lithium or anticonvulsants used as mood stabilizers. If antidepressants are used, SSRIs should be preferred due to their lower risk of a switch risk to mania (Goodwin et al. 2003, Grunze et al. 2010b, Möller 2006a). If the prescription of TCAs, which induce a switch to mania in about 10 % of patients, is deemed clinically necessary, co-medication with a mood stabilizer is recommended to reduce the risk of switching to mania. Some experts and guidelines recommend not to administer antidepressants in bipolar depression at all, but to predominantly use mood stabilisers instead (Yerevanian et al. 2007b). Some authors suggested that the induction of suicidality by antidepressants in bipolar patients might be related to the induction of depressive mixed states or hypomania/mania (Rihmer and Akiskal 2006. Rihmer 2007).

At least in mixed states, i.e. the coexistence of depression and manic symptoms (Balazs et al. 2006), as well as in patients with rapid cycling, antidepressants should be completely avoided; in such cases, treatment has to rely on lithium or other mood stabilizers only. Based on recently published data on olanzapine and quetiapine (Calabrese et al. 2005, Perlis 2007, Perlis et al. 2006), it appears that these and possibly other atypical neuroleptics will become more and more an option for the treatment of patients suffering from an acute depressive episode in the frame of a bipolar affective disorder.

Schizophrenia

Schizophrenia has a more or less similar lifetime risk for suicide as unipolar or bipolar depression. The symptoms of schizophrenia can be easily treated with antipsychotics (Falkai et al. 2005). Especially second generation antipsychotics are increasingly in use in recent years because of their lower liability to extrapyramidal side effects and a broader spectrum of efficacy (Möller 2002, 2000). Suicidality associated with a schizophrenic psychosis often requires medication in addition to the standard neuroleptic

treatment of the schizophrenic symptoms, especially in cases of severe anxiety or excitation. Sedating neuroleptics or benzodiazepines are indicated in these conditions.

A different approach is required for suicidality in schizophrenic patients who have depressive or negative symptoms. If depressive-apathetic symptoms with suicidality exist as part of a postpsychotic depression or a deficit syndrome, pharmacotherapy should generally follow the guidelines for the treatment of these conditions. This means that treatment with antidepressants in the case of depressive syndrome, and treatment with atypical neuroleptics or SSRIs (or both) in the deficit syndrome, is necessary (Möller 2006a, 2005b, 2006a; Möller et al. 2006). If the suicidal symptoms are a side effect of treatment with classical neuroleptics (pharmacogenic or akinetic depression), the neuroleptic dose should be reduced, if possible, or the patient should be switched to an atypical neuroleptic. An antiparkinson drug such as biperidon might often be advisable for some days to reduce the parkinsonian side effects as soon as possible.

Atypical antipsychotics are the treatment of choice for long-term relapse prevention in schizophrenia, especially those with depressive/suicidal features, because they have no or a lower risk of inducing depression compared to the first generation antipsychotics, and may even have antidepressant effects (Möller 2005b, 2005a). Atypical neuroleptics thus possibly reduce not only depression, but also related suicidality. Of special interest is that clozapine seems to have a special antisuicidal efficacy in the long-term treatment of schizophrenic patients (Meltzer et al. 2003, Meltzer and Okayli 1995). The study of Spivak and co-workers (Spivak et al. 2003) suggests that the reduction in suicidality following long-term clozapine treatment may be related to a reduction in impulsiveness and aggression. Interestingly for olanzapine such a suicide-preventive effect could not be demonstrated in a study (Meltzer et al. 2003)

Anxiety disorders and obsessive-compulsive disorders

Anxiety disorders are often associated with the risk of suicidality. In addition to psychotherapeutic procedures, nearly all anxiety disorders and obsessive compulsive disorders (OCD) are an indication for psychopharmacological treatment. Serotonergic antidepressants, especially SSRIs, are the treatment of choice, but also the dual selective reuptake inhibitor venlafaxine has demonstrated efficacy in anxiety disorders (Bandelow et al. 2008). If suicidality occurs during such disorders, monotherapy with an antidepressant is often not sufficient to overcome the critical situation quickly enough. Short-term administration of benzodiazepines or sedative neuroleptics along with the antidepressant may be necessary. However, the application of a benzodiazepine should be restricted to a short period of days or a few weeks to avoid the risk of a dependency.

Personality disorders

Personality disorders are frequently associated with chronic, repetitive suicidality. At special risk are histrionic and borderline patients. In general, the efficacy of psychopharmacological treatment of personality disorders is not well established (Kapfhammer and Hippius 1998, Herpertz et al. 2007, Cardish 2007). In borderline cases, the occasional risk of paradoxical reactions to benzodiazepines or TCAs and possibly also to modern antidepressants like the SSRIs should be taken into consideration (Möller 1994b). In most cases, only pharmacological treatment of the acute critical condition seems indicated. Benzodiazepines, antidepressants with a sedative-anxiolytic profile or low potency neuroleptics in low dosages can be administered in this indication as a short-term intervention. It should be taken into account that these suggestions are mostly based on clinical experience, but not on clinical trials. Long-term treatment with benzodiazepines should be avoided due to the risk of abuse.

Over the last years atypical neuroleptics have gained more widespread use for patients with BPD and seems to have promising effects on impulsivity and suicidal behaviour (Hilger et al. 2003, Zanarini and Frankenburg 2001) especially when they are used in combination with psychotherapeutic measures (Soler et al. 2005).

There are only very few studies that have investigated whether a medium-term psychopharmacological approach might be useful in the prevention of further suicide attempts in patients with a history of repeated suicide attempts. The studies that have been performed have mostly involved patients suffering from co-morbidity with personality disorders of the impulsive, histrionic and borderline type (Montgomery et al. 1992).

Adjustment disorders and post-traumatic stress disorders

When suicidality results from abnormal reactions to psychosocial stress, psycho-pharmacological interventions are mainly aimed at sedation, anxiolysis, sleep induction or suppression of disturbing vegetative symptoms.

Anxiolytic benzodiazepines, or in cases of predominant sleep disturbances sleep-inducing benzodiazepines or the modern non-benzodiazepine hypnotics, are generally the treatment of first choice in adjustment disorders. The selection of the specific compound and of the dose varies according to the individual case. The aim should be to induce not only sedation but also affective-emotional distancing. Some doctors tend to be very restrictive in prescribing benzodiazepines, even under these conditions, because they have concerns regarding the risk of dependency. They prefer to use sedating antidepressants, such as doxepin, or low doses of sedating neuroleptics as surrogates. However, given the extraordinary good tolerability of benzodiazepines and the high compliance of patients with these drugs, the risk-benefit assessment should favour the benzodiazepines under these special conditions, especially given the fact that, in general,

only short-term medication is needed. An inadequate psychopharmacological regime could induce a high risk of continuation of suicidality, and for this reason undertreatment with benzodiazepines, which seems to become a general problem in patients with a need for benzodiazepine treatment (Möller 1999), should be avoided. In cases of longer-lasting depressive reactions, antidepressants should be considered. Modern antidepressants with better tolerability than the TCAs should preferably be chosen.

The psychopharmacological treatment of post-traumatic stress disorder is not yet well defined. Most experts recommend SSRIs, while benzodiazepines are not seen to be effective (Ursano et al. 2004, Davidson 2004, Asnis et al. 2004).

5. Conclusions

Psychiatric disorders can cause suicidality. Given the high prevalence and lifetime risk of depressive disorders, depression is one of the major causes of suicidal behaviour. Adequate psychopharmacological treatment of depression and other psychiatric disorders associated with suicidality is recommended as a meaningful strategy to reduce suicidal thoughts and suicidal behaviour. Depending on the individual disorder and the specific conditions, this includes the administration of antidepressants, antipsychotics, benzodiazepines and hypnotics. The psychopharmacological intervention should aim to have a positive effect on the suicidality as soon as possible. In critical situations, co-medication is often clinically indicated, e.g. the combination of an antidepressant with a benzodiazepine.

The findings of randomised, control group studies in acute depressive patients supply evidence that antidepressants are able to reduce suicidal thoughts in depressive patients. However, data from such studies give no support to the hypothesis that antidepressants can reduce suicide attempts or suicide. The low base 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 data sets from randomised controlled trials seem unable to overcome this problem. Thus, complementary methodological approaches such as pharmacoepidemiological studies have to be applied. The latter demonstrated positive results on the effectiveness of antidepressants in the prevention of suicide.

Over the past year there have been intensive discussions about possible negative effects of antidepressants on suicidality. Although there is only weak evidence for such effects, and this especially for young patients, the potential but rare risk of inducing suicidality should be considered carefully. An optimal clinical management can avoid possible harmful consequences of treatment with antidepressants.

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