Completed Suicides in 47 Psychiatric Hospitals in Germany – Results from the AGATE-Study

Authors

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Key words
- suicide
- psychopharmacotherapy
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- AGATE study

Abstract

Introduction: There is an ongoing debate about a possibly enhanced risk of suicidal behaviour in some psychiatric patients due to psychopharmacotherapy. Our retrospective study aimed at analyzing the psychopharmacotherapy of 133 inpatient suicides and 133 controls by a matched pair design.

Methods: We analyzed all suicides (n = 133) reported in the AGATE study from 1991 to 2008. Besides evaluation of sociodemographic variables and suicide methods, we compared psychopharmacotherapy of suicides with schizophrenia (n = 59) and affective disorders (n = 59) to that of a matched control group.

Results: Most suicides (n = 102, 76.7 %) were judged not to be related to psychopharmacotherapy. In general, more psychopharmacological drugs were prescribed for suicides than for controls. Schizophrenic suicides received more low potency FGAs than their controls. More suicides with affective disorders than controls were treated with NASSAs, SNRIs, and high or low potency FGAs. In contrast to their controls, none of the suicides with affective disorders received lithium. NASSAs, SNRIs, and high or low potency FGAs predicted suicide in regression analysis for inpatients with affective disorders.

Discussion: Differences in psychopharmacotherapy might mainly result from a recognized risk of suicide or a more severe degree of illness. However, the underrepresentation of lithium in the suicide groups is noticeable.

Introduction

Suicide is a tragic event which cannot always be prevented in spite of all efforts. This is also true for psychiatric hospitals with professional staff knowing about and dealing with an enhanced suicide risk of psychiatric patients. With about 0.06 to 5.66 suicides per 1 000 admissions [1] suicide is a rather rare event during psychiatric inpatient care. In spite of the relatively rare occurrence of suicide in psychiatric hospitals, many risk factors for inpatient suicide are well-

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AGATE: Arbeitsgemeinschaft Arzneimitteltherapie bei psychiatrischen Erkrankungen

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established, e.g., previous suicidal behaviour, depressive symptoms or early stage of inpatient stay [1,2]. Highest suicide risk is usually found for inpatients with schizophrenic or affective disorders, which respectively account for up to 75% of inpatient suicides [1–8].

Since an increase of suicidal thoughts and suicide attempts was found for children and adolescents taking antidepressants, attention turned to psychopharmacotherapy – initially focusing on SSRIs – as a potential risk factor of suicide [9–11]. Consequently, the U.S. Food and Drug Administration (FDA) required a black box warning regarding such a risk in patients up to the age of 24 years [9,10,12,13]. Some studies reported enhanced risk also for adults, whilst others could not find any evidence for antidepressant-induced suicidality [14–16]. Among others, the suicidality-antidepressant link is supposed to result from energizing depressed patients to act on pre-existing suicidal thoughts or impulses before reversing their depressed mood or paradoxically worsening depression in some patients [16–18]. Furthermore, antidepressant monotherapy without applying mood stabilizers may favour switching patients into manic or mixed states or worsen pre-existing unrecognized pseudo-unipolar mixed states [18,19]. In this context, it had even been hypothesized that depressive mixed state may overlap considerably with the so-called "antidepressant activation syndrome" [20]. Altogether, there seems to be a small amount of evidence that antidepressants might increase the risk of suicide thoughts or attempts, especially in children and adolescents, whereby an increased risk of completed suicide has not been found until now [14,16–17]. However, some aspects concerning drug-induced suicidality may not be specific to antidepressants. Treatment resistance was found to increase the risk of attempted and completed suicide in a sample of adult psychiatric inpatients, possibly by inducing resignation and hopelessness regarding recovery or enduring psychopathology [5]. Furthermore, some side effects of psychopharmacology, e.g., akathisia, akinesia, agitation, or insomnia are under discussion to enhance not only the risk of attempted, but even the risk of completed suicide [4,5,16–18,21–23].

The aim of our retrospective case-control study was to analyze psychopharmacological treatment of inpatient suicide victims at the time of suicide by using a psychopharmacological database comprising data of 47 psychiatric hospitals in Bavaria, Southern Germany. As each suicide had been discussed in case conferences by experts, the frequency of suicides attributable to psychopharmacological treatment was also considered. Because of their enhanced risk of suicide, our study focused on inpatients with schizophrenic and affective disorders.

Patients and Methods

Data base

The Working Group "Drugs in Psychiatry" (AGATE) is a consortium of 47 psychiatric hospitals located in Southern Germany caring for quality assurance in psychopharmacological treatment [24]. Suicides are documented by using a standardized protocol for spontaneous reporting of adverse events of psychopharmacotherapy. Besides age, gender, diagnosis, admission date and onset of disease, medication and – for most cases – dose at the time of suicide are also recorded. For most cases, a description of suicide method is added in free text. Furthermore, the likelihood of the suicide to be drug-induced is rated for each applied psychopharmacological drug in case conferences of the AGATE representatives taking place every two months (0="no relation", 1="possibly related", 2="probably related", 3="surely related", 4="cannot be assessed"). From 1991 to 2008 133 suicides were registered in the database.

Since 1995, pharmacotherapeutical treatment is documented in the hospitals affiliated to AGATE twice a year on due dates (April, October). For each patient hospitalized on due dates, pharmacotherapy on due date and basic socio-demographic and disease-related data (gender, age, psychiatric and somatic diagnosis according to ICD-9/ICD-10) are reported by the local AGATE representative in a standardized protocol. From 1995 to 2008, 123 086 inpatients were registered in the AGATE database. This data pool was used to extract matched controls for the suicides.

Table 1 Classification of psychopharmacological drugs.

Psychopharmacological category
first-generation antipsychotics (***FGAs***): low, medium, high potency
second-generation antipsychotics (***SGAs***): sedative, non-sedative
tricyclic antidepressants (***TCAs***): sedative, non-sedative
selective serotonin reuptake inhibitors (***SSRIs***)
serotonin-norepinephrine reuptake inhibitors (***SNRIs***)
norepinephrine (noradrenaline) reuptake inhibitors (***NRIs***)
norepinephrine-dopamine reuptake inhibitors (***NDRIs***)
noradrenergic and specific serotonergic antidepressants (***NASSAs***)
monoamine oxidase inhibitors (***MAO-Is)***
other antidepressants (***OAs***)
lithium (***LI***)
benzodiazepines (***BZDs***)
other hypnotics (***OHs***)
antiepileptics (***AEPs***)
anti-dementia drugs (***ADDs***)
antiparkinson drugs (***APDs***)
other psychopharmacological drugs (***OPDs***)
thyroid drugs (***TDs***)

Matching procedure

For each suicide a control patient matched by age, gender, diagnosis and year of admission was selected. If several potential controls were available, the control subject was chosen randomly. In the case of none of the control subjects met all 4 matching criteria of the suicide exactly, the control subject with the age nearest to the suicide was chosen. Gender, diagnosis and year of admission could be matched exactly for each suicide with the following exceptions: as suicide data ranged from 1991–2008 and control data from 1995–2008, 1995 was selected as control year for all suicides from 1991 – 1994 (n = 31). Gender was not specified for 1 suicide and was matched randomly for that case. Diagnosis was not specified for 1 suicide; for another suicide, diagnosis could not be matched as it was not present in the control group. Thus, diagnosis was matched randomly for these 2 cases.

Psychopharmacotherapy

Psychopharmacological drugs were grouped into categories, whereby potency and sedative effects were also considered (◉ **Table 1**).

Statistical analyses

Data were analyzed by PASW Statistics 18. Suicides and control subjects were described regarding their sociodemographic and disease-related data. Methods of completed suicides were analyzed gender specific by using the chi-square test.

To consider psychopharmacological treatment of most frequent diagnoses separately, all suicides with schizophrenic (n = 59, 44.4%) or affective (n = 59, 44.4%) disorders (**Table 2**) were compared to their respective controls by using chi-square tests, Fisher's exact tests and T tests. Logistic regression analyses were performed to explore possible risk factors for inpatient suicide. Thereby, all variables with a significant result in bivariate analyses were entered as independent variables.

Results

Inpatient suicides and control group

The majority of inpatient suicides was male (n = 77, 57.9%), 41.4% (n = 55) female, for 1 suicide (0.8%) gender was not specified. Mean duration of illness of suicides was 12.77 years (*SD* = 11.32), mean age of suicides was 47.22 years (*SD* = 14.98).

Table 2 Diagnostic spectrum of suicide completers (n = 133).

Diagnosis	n	%
schizophrenic disorder (ICD-9: 295, ICD-10: F20-F25.9)	59	44.4
affective disorder (ICD-9: 296, ICD-10: F30-F39)	59	44.4
personality disorder (ICD-10: F60-F61)	4	3.0
mixed diagnostic categories (ICD-9: 300–316)	4	3.0
organic affective disorder (ICD-10: F06.3)	2	1.5
alcohol dependence syndrome(ICD-10: F10.2)	1	0.8
panic disorder (ICD-10: F41.0)	1	0.8
mixed anxiety and depressive disorder (ICD-10: F41.2)	2	1.5
unknown	1	0.8
total	133	100.0

There was no difference regarding age at suicide between males and females ($M = 47.01$ vs. $M = 47.13$, $T = -0.043$, $p = 0.966$). Mean age of controls was 46.86 years (*SD* = 15.06). For male controls mean age was 46.46 years (*SD* = 16.05), for female controls 47.42 years (*SD* = 13.67). Most frequent methods of suicide were jumping from height (29.3%), hanging (21.8%) and vehicular impact (17.3%) (**Table 3**). There was no difference regarding method of suicide by gender ($\chi^2 = 14.374$; $p = 0.277$).

Psychopharmacotherapy

Total sample

With the exception of 5 control patients, all patients in the suicide and control samples, respectively, received psychopharmacotherapeutical drug treatment during the index time. Mean daily dosages for the drugs most often prescribed are shown in **Table 4**.

Most suicides (n = 102; 76.7%) were not attributed to psychopharmacotherapy. 7 suicides (5.3%) were judged to be possibly related to psychopharmacotherapy. Of these, all 7 suicides received more than 1 psychotropic drug. For 2 cases SSRIs were suspected to be associated with the suicide, for 3 other cases SNRIs, TZAs or MAO-Is. A combination of SSRIs with NASSAs or with sedative SGAs was suspected in the 2 other cases. There was only 1 suicide (0.8%) judged to be probably associated with psychopharmacotherapy taking a combination of BZD and TCA. For 23 suicides (17.3%), the relation to psychopharmacological treatment could not be assessed.

Table 3 Methods of suicide completers (n = 133).

	Total		Females		Males	
Method	n	%	n	%	n	%
jumping from height	39	29.3	21	38.2	18	23.4
hanging	29	21.8	9	16.4	20	26.0
vehicular impact	23	17.3	9	16.4	14	18.2
drowning	14*	10.5	8	14.5	5	6.5
poisoning/overdose	8	6.0	3	5.5	5	6.5
strangulation	7	5.3	1	1.8	6	7.8
stitch damage	1	0.8	0	0.0	1	1.3
unknown	7	5.3	1	1.8	6	7.8
others	5	3.8	3	5.5	2	2.6
total	133	100.0	55	100.0	77	100.0

*Gender not specified for one suicide completer

Table 4 Mean daily dosages: suicides (n = 133) vs. controls (n = 133).

	Suicides		Controls	
	Dosage [mg/d]	n*/n[a]	Dosage [mg/d]	n
Lorazepam	2.15 mg/d (SD = 2.03)	60/31	1.52 mg/d (SD = 0.99)	39
Mirtazapine	40.18 mg/d (SD = 15.46)	33/14	40.38 mg/d (SD = 16.64)	13
Haloperidol	9.48 mg/d (SD = 9.18)	28/23	7.75 mg/d (SD = 5.55)	8
Risperidone	4.71 mg/d (SD = 1.70)	17/7	2.85 mg/d (SD = 1.52)	13
Carbamazepine	550.00 mg/d (SD = 181.87)	21/14	530.00 mg/d (SD = 221.36)	10
Amitriptyline	98.08 mg/d (SD = 50.85)	15/13	125.00 mg/d (SD = 41.64)	20
Biperiden	3.50 mg/d (SD = 1.08)	14/10	3.86 mg/d (SD = 1.46)	14
Clozapine	339.06 mg/d (SD = 289.20)	9/8	297.06 mg/d (SD = 169.18)	17
Doxepin	141.67 mg/d (SD = 149.75)	18/12	121.43 mg/d (SD = 41.90)	7
Olanzapine	12.50 mg/d (SD = 4.47)	12/6	13.13 mg/d (SD = 7.00)	12
Melperone	107.50 mg/d (SD = 58.98)	17/10	100.00 mg/d (SD = 114.56)	5
Citalopram	27.00 mg/d (SD = 14.18)	17/10	36.67 mg/d (SD = 13.66)	6

[a]Dosages were not reported for some suicide cases: n* = number of cases receiving respective medication, n[a] = numbers with dosage listed

Table 5 Psychopharmacotherapy of suicides with schizophrenic disorders (n = 59) vs. controls (n = 60)[a,b].

	Suicides	Controls	χ^2	Significance p
FGAs				
Total	41	34	2.100	0.147
Low potency	22	12	4.357	**0.037**
Medium potency	8	7	0.097	0.756
High potency	39	26	0.674	0.412
SGAs				
Total	33	29	0.688	0.407
Sedative	21	21	0.005	0.946
Non-sedative	16	9	2.633	0.105
TCAs				
Total	8	8	0.001	0.971
Sedative	8	7	0.097	0.756
SSRIs	7	10	0.560	0.454
LIs	3	6	1.028	0.311
BZDs	26	17	3.191	0.074
AEPs	13	8	1.550	0.213
APDs	12	15	0.368	0.544

[a] Abbreviations listed in **Table 1**

[b] Chi-square test not computed for non-sedative TCAs, SNRIs, NRIs, NDRIs, NASSAs, MAO-Is, OAD, OHs, ADD, OPDs, TDs (≤ 5 cases)

Table 6 Psychopharmacotherapy of suicides (n = 59) with affective disorders versus controls (n = 60)[a,b].

	Suicides	Controls	χ^2	Significance p
FGAs				
Total	27	18	3.143	0.076
Low potency	16	7	4.555	**0.033**
Medium potency	5	6	0.083	0.774
High potency	15	6	4.869	**0.027**
SGAs				
Total	14	20	1.345	0.246
Sedative	10	13	0.425	0.515
Non-sedative	4	7	0.847	0.357
TCAs				
Total	23	25	0.089	0.765
Sedative	19	19	0.004	0.950
Non-sedative	8	7	0.097	0.756
SSRIs	15	16	0.024	0.877
SNRIs	10	3	4.365	**0.037**
NASSAs	22	11	5.333	**0.021**
MAO-Is	4	4	0.001	0.980
LIs	0	12	13.123	**0.000**
BZDs	37	29	2.490	0.115
OHs	11	10	0.080	0.777
AEPs	10	7	0.678	0.410
OPDs	3	5	0.501	0.479
TDs	2	8	3.821	0.051

[a] Abbreviations listed in **Table 1**

[b] Chi-square test not computed for NRIs, NDRI, OAD, ADD and APDs (≤ 5 cases)

Suicides with schizophrenic disorders

Significantly more psychopharmacological drugs were applied to schizophrenic suicides (n = 59) than to their controls (n = 60) ($M = 3.44$ vs. $M = 2.58$, $T = -3.371$, $p = 0.001$). Schizophrenic suicides received a higher number of antipsychotics ($M = 2.05$ vs. $M = 1.35$, $T = -4.166$, $p = 0.000$), but not more antidepressants ($M = 0.37$ vs. $M = 0.37$, $T = -0.061$, $p = 0.951$). There were only 3 controls and 1 suicide without antipsychotic treatment. Low potency FGAS were significantly more often prescribed to schizophrenic suicides than controls (**Table 5**). No regression model could be established for schizophrenic suicides.

Suicides with affective disorders

Suicides with affective disorders (n = 59) received a higher number of psychopharmacological drugs ($M = 3.76$ vs. $M = 3.05$, T = −2.580, $p = 0.011$) and antidepressants ($M = 1.59$ vs. $M = 1.03$, T = −3.929, $p = 0.000$), but not more antipsychotics ($M = 0.92$ vs. $M = 0.72$, T = −1.503, $p = 0.136$) than the controls (n = 60). 1 suicide and 5 controls were without antidepressants or mood stabilizers. Significantly more suicides than controls were treated with SNRIs, NASSAs and high or low potency FGAs. In contrast to their controls, none of the suicides received lithium (**Table 6**). Because none of the suicides received lithium, lithium could not have any influence on the probability function of the regression model and could therefore not be included in the regression analysis. Regression analysis identified SNRIs ($OR = 5.229$, $p = 0.025$, 95 % CI: 1.234 – 22.167), high potency FGAs ($OR = 4.197$, $p = 0.012$, 95 % CI: 1.372 – 12.837), NASSAs ($OR = 3.968$, $p = 0.003$, 95 % CI: 1.581 – 9.959) and low potency FGAs ($OR = 3.418$, $p = 0.023$, 95 % CI: 1.180 – 9.898) as predictors of inpatient suicide. The variables explained 23.8 % of variance.

Discussion

As in many other studies considering inpatient suicides [1–8, 25], schizophrenia and affective disorders were the most common diagnoses of the suicide cases with almost 45 %, respectively. If overdoses, poisoning and gas were classified as non-violent suicide methods, almost all of the suicide completers (94 %) used violent methods as it is commonly found in psychiatric hospitals [3, 7, 8, 25, 26]. Death as a consequence of poisoning by psychotropic drug overdose was rare and documented for only 6 inpatients, amongst them lithium was used by 1 inpatient. Most suicides (76.7 %) were not attributed to psychopharmacotherapy by the AGATE representatives in the case conferences, only 8 suicides were judged to be possibly (n = 7) or probably (n = 1) related to psychopharmacological treatment. This argues against a remarkably high proportion of suicides induced by psychopharmacotherapy. In general, suicides received a higher number of psychotropic drugs and less often monotherapeutic treatment. This may correspond to a more severe degree of illness.

Suicide victims with schizophrenia

The only difference between the suicide and the control group was that suicides received significantly more often low potency FGAs. Suicides were also prescribed more often benzodiazepines than controls (26 vs. 17), but this result did not reach significance level. As the use of psychotropic drugs with sedative effects, e.g., benzodiazepines or low potency FGAs, is recommended for treatment of acute suicidal crisis, it seems reasonable that suicidality could have led to rather than resulted from treatment with low potency FGAs or benzodiazepines. If that were the case, realization of suicidal ideas and plans could not be prevented for these patients by adequate pharmacological treatment. Higher use of benzodiazepines in suicides has been found in other studies and particularly the reduction or withdrawal of benzodiazepines was supposed to be critical [25, 27].

In general, treatment with antipsychotics goes along with a lower mortality and suicide risk for patients with schizophrenia [28–31]. Correspondingly, suicide risk is considerably increased in patients with poor adherence to medication [32–34]. The

positive association of duration of untreated psychosis (DUP) with suicide risk and the high suicide risk in the first few years after diagnosis highlight the importance of early pharmacological treatment for suicide prevention [35–37]. Apparently, suicide risk reduction does not result from treatment success for positive symptoms, but is rather associated with treatment of negative symptoms, e.g., specific affective symptoms [32,33,37]. However, an increased risk of all-cause mortality and suicide was shown in users of thioxanthenes [38]. Beneath a real suicide-risk enhancing effect, a prescription bias, e.g., because of comorbid depression, was suspected [38]. Some authors point to an increased suicide risk due to awareness of illness, whereby improvement of symptoms also resulting from antipsychotic treatment may paradoxically lead to enhanced risk of suicide [39–41].

Furthermore, an antipsychotic dose-suicide relationship has to be considered, which is supposed to follow an inverted "U": While very low doses might be ineffective and therefore not affect suicide risk, choice of high doses might be a proxy indicator of the severity of disease or treatment resistance and lead to side effects [35,42] which can produce suicidality in at least some patients, e.g., extrapyramidal side effects (EPS) [4,21,22]. It is also under discussion as to whether antipsychotics can directly induce depression as a side effect [21,22]. In our sample, we could not find a difference between suicide cases and controls regarding application of antidepressants and antiparkinson drugs or remarkable variations in dosages with the exception of the risperidone dosage being higher in the suicide group. Likewise in another study [25] no difference was found between schizophrenic suicides and controls regarding choice of drug, potency or dosage for antipsychotics. However, in that study [25] suicides received more often antidepressants, but less often mood stabilizers whereby mood stabilizers were supposed to be superior to antidepressants in patients with predominant depressive symptoms. In our sample, suicides did not differ from controls regarding the application of antidepressants and mood stabilizers. This may result either from an adequate treatment of depression or from a higher percentage of untreated or even unrecognized depressive symptoms in the suicide group [25].

As it was recommended for psychopharmacological management to minimize side effects, especially EPS and akathisia, atypicals were suggested to be used in first line on the basis of their advantageous side effect profile [28]. Especially clozapine seems to be a valuable therapeutic option for reducing suicidal behaviour [43] and should receive early consideration when suicidality is a major concern. We conducted analyses also separately for clozapine use, but could not find a difference between the suicide and the control group. However, as only 9 schizophrenic suicides and 14 controls received clozapine, the number of cases may have been to low to detect significant differences.

Suicide victims with affective disorders

High and low potency FGAS, SNRIs and NASSAs were more often prescribed in the suicide group than in the control group and evolved as predictors of suicide in the regression model. Furthermore, none of the suicides, but 12 controls received lithium. The higher incidence of low and high potency FGAs in the suicide group was not protective in this population, as it has also been found in another case-control study [25]. Application of low potency agents seems adequate to bridge suicidal crisis and may have resulted from recognition of acute suicidality or to counteract agitation. As proportion of high potency first generation antipsychotics was also higher in the suicide group, this may give evidence to a different symptomatic profile. As we matched for diagnosis, there was no difference regarding incidence of psychotic depression or bipolar disorders. May be there was a higher proportion of patients with mixed state of depression in the suicide group which accounted for treatment trials with FGAs. As a mixed state of depression is under discussion to be a precursor of suicidal behaviour, unrecognized cases of bipolar depressives may be at particular risk as antidepressant pharmacotherapy unprotected by mood stabilizers or atypical antipsychotics can worsen the clinical state [19,20].

Another explanation would be inadequate treatment of bipolar disorders with antipsychotics at the costs of mood stabilizers and it is worth having a closer look at these patients. There were respectively 13 patients with bipolar disorder in the suicide and control groups. Whereas 7 patients of the control group received lithium, none of the suicides did. Furthermore, 8 suicide victims and 5 controls received AEPs. High potency FGAs were received by 4 suicides and 2 controls, but were used in combination with AEPs, which argues against an application of antipsychotics at the costs of mood stabilizers. However, the underrepresentation of lithium is remarkable. None of the suicide completers had received treatment by lithium (control group: n=12), which may hint at the suicide preventive effect of lithium found in many other studies [44–47]. A meta-analysis of randomized trials suggested that the risk of suicide was significantly reduced in people with affective disorders taking lithium [45]. Possible mechanisms of antisuicidal action include its effects on mood stabilization, impulsivity and aggression and a non-specific effect arising from close long-term monitoring [44].

Regarding antidepressant agents the only differences we could find were that NASSAs and SNRIs were more often applied to suicide victims and evolved as predictors of suicide risk. Application of SNRIs enhanced risk of suicide about 5-fold for inpatients with affective disorders. 9 out of 10 suicide victims and all controls taking SNRIs were prescribed venlafaxine, for 1 suicide case a combination of nefazodone and duloxetine was documented. However, in the AGATE case conferences there was only 1 suicide case taking venlafaxine for which suicide was possibly attributed to the use of a SNRI, indicating that experts did not suspect a causal relationship of SNRIs to suicide in the majority of cases. In another study, venlafaxine was associated with a higher suicide risk in comparison to citalopram, fluoxetine, and dothiepine, which could give evidence for a causal relationship [48]. Most of this risk was attributable to confounding factors, i.e., the prescription of venlafaxine to patients with more severe or difficult to treat depression and with a higher burden of risk factors for suicide [48,49]. Even if there seem to be individual cases with an emergence of suicidal behaviour after starting or increasing duloxetine [50], no evidence of an increased risk of suicidal behaviours or ideation was found in other studies [51,52]. This calls a potential association of SNRIs with suicidal behaviour into question and complicates a coherent conclusion.

Usually, sedative antidepressants are preferred to activating antidepressants in the treatment of suicidal patients. Conform to this, twice as many suicides (n=22) as controls (n=11) received NASSAs, in all cases mirtazapine. Thereby, recognition of suicidality might have led to adequate psychopharmacological treatment, but the sedative and sleep inducing effect of mirtazapine could not prevent suicide. However, our suicides and controls received rather high doses of mirtazapine (~40 mg/d) and the sedative effect of mirtazapine may have been superim-

posed by the increasing noradrenergic effect in higher doses. The relation of mirtazapine and suicidal behaviour is not unambiguous: An analysis of antidepressant placebo-controlled trials in pediatric patients included also a mirtazapine study in major depressive disorder and showed an enhanced relative risk for suicidal behaviour or ideation [10]. In a meta-analysis, mirtazapine was associated with a risk reduction of self-harm and suicide-related events in children and adolescents with depression, but results for individual drugs were restrained by small numbers and few incidences of adverse events [53]. A longitudinal analysis of suicidal behaviour risk basing on 15 placebo-controlled randomized studies of mirtazapine in major depression showed short-term treatment of mirtazapine to be associated with a reduced suicidality risk compared to placebo as measured by the HAMD suicide item scores [54].

In a meta-analysis of 372 placebo controlled trials the risk of suicidal thoughts or behaviour associated with the use of antidepressants was strongly age-dependent, whereby a continuous reduction in risk associated with treatment with age was found [55]. Higher risk associated with antidepressant treatment compared to placebo was found for those aged under 25, but lower risk in those aged 25 or older. The net effect of antidepressants seemed protective for adults aged 25 or older. This meta-analysis also did not show much evidence for differences between antidepressants in net effect on suicidality. Altogether, the benefits of antidepressants outweigh the risk, especially for adults [16,17,55].

Limitations

As our retrospective study examined the status quo of psychopharmacotherapy at the time of suicide in comparison to a control group, it is impossible to draw any causal conclusions, e.g., suicide-inducing or protective effects of psychopharmacological drugs. Furthermore, suicide data were obtained in the context of a spontaneous reporting system of adverse events, whereby an estimated number of unreported adverse events of about 80% has to be assumed [56]. Prescription behaviour and treatment conditions may vary between the hospitals affiliated to AGATE. Also, the study periods of our samples did not overlap completely, as suicide data ranged from 1991–2008 and control data from 1995–2008. Therefore, 1995 had to be selected as control year for 31 suicides from 1991–1994. As novel psychopharmacological drugs were introduced to the market during our study period, a bias for the years 1991–1994 cannot be excluded. Information about relevant suicide risk factors was not available and we could not consider psychopathology or preceding suicidal behaviour or thoughts in our analyses. Due to the small numbers, results for individual drugs were restricted to the information about mean daily dosage of the drugs most often prescribed. Further data regarding dose distribution over time were not available so that we did not have any information about augmentation, withdrawal, and switching at the time of suicide. Our sample size was rather small, but as data were obtained from 47 German psychiatric hospitals, results may reflect psychopharmacotherapy at the time of suicide for inpatient suicides in Southern Germany.

Conclusion

Most differences in medication may be explainable by pharmacological treatment of suicidality or by a more severe degree of illness in the suicide groups. However, the rare use of lithium in the group of affective suicides was obvious. Although psychopharmacotherapy is an important means of suicide prevention, suicides cannot always be prevented even if psychopharmacotherapy would be adjusted optimally under consideration of suicide risk. Suicide prevention in psychiatric hospitals requires more than psychopharmacotherapy: psychotherapeutic interventions and psychosocial support are compulsory and should be maximized, also to improve compliance with treatment.

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