Suicidality as Rare Adverse Event of Antidepressant Medication: Report From the AMSP Multicenter Drug Safety Surveillance Project

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Objective: Since the advent of antidepressant drug treatment, the question of whether these substances induce suicidal ideation and behavior has not been satisfactorily answered. The aim of this study is to contribute to this ongoing discussion by taking a heuristic case-based approach to the question.

Method: A large data set from a European drug surveillance program (Arzneimittelsicherheit in der Psychiatrie; AMSP) performed in 85 psychiatric hospitals from 1993 until 2008 was analyzed. A series of single cases were carefully assessed. The observed frequencies of adverse drug reactions (ADRs) in this sample were related to the total AMSP population, who used the imputed medication.

Results: A total of 142,090 adult patients taking antidepressant medication were observed. Thirty-three incidents of suicidality (12 cases of suicidal ideation, 18 attempts, and 3 completed suicides) were documented. Fourteen cases were assumed to be probably, and 19 to be possibly, related to the drug. Twenty-three cases judged as suicidal ADRs were associated with restlessness, 10 with ego-dystonia, 9 with impulsiveness, and 3 with psychosis. A higher incidence of suicidal ADRs was observed for selective serotonin reuptake inhibitors (0.034%; 95% CI, 0.020–0.054) and serotonin-norepinephrine reuptake inhibitors (0.034%; 95% CI, 0.015–0.068) compared to noradrenergic and specific serotonergic antidepressants (0.009%; 95% CI, 0.002–0.027) and tricyclic antidepressants (0.002%; 95% CI, 0.000–0.014).

Conclusion: Despite the methodological limitations of this study, the large AMSP data set supports the assumption that antidepressant drugs rarely trigger suicidality.

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Pharmacoepidemiologic studies have shown that an increase in the prescription rate of antidepressant drugs is associated with a decreased risk of suicide. This holds true for large epidemiologic studies linking prescription data with suicide data, as well as for special intervention studies (eg, "Gotland Study," "Nürnberger Modell," "Zurich Follow-up Study"; for reference, see Möller[1]).

Nevertheless, some earlier observations suggested that there was a connection between the initiation of treatment with the tricyclic antidepressant imipramine[2] or later on with the selective serotonin reuptake inhibitor (SSRI) fluoxetine[3] and the emergence of suicidal ideation. Furthermore, Rouillon and colleagues[4] reported significantly higher numbers of suicide attempts by patients on long-term treatment with the tetracyclic antidepressant maprotiline compared to placebo. Additionally, suicidal attempts were observed in the context of psychomotor activation in connection with less sedative antidepressants.[5,6] Finally, suicidality was linked to some cases of antidepressant drug–induced psychosis.[6]

In the last few years, the discussion has focused more on suicidality in connection with SSRIs, mainly in children and adolescents[7] but also in adults.[7–9] The increase of suicidal behavior during antidepressant medication was attributed to a so-called drive-mood dissociation and to the disinhibition of impulsive behavior.[10–13] Nevertheless, it is still difficult to decide whether suicidal behavior is an "adverse effect" of the medication or a "symptom" of the disease. Some experts fear that an overcritical attitude to antidepressants could increase the number of suicides due to undertreatment.[11,14]

The degree of suicidal risk reported so far depends on the method of the study,[1] patient characteristics such as age, personality traits and diagnoses, the type of suicidality examined[11,15] (ie, suicidal ideation, suicide attempt, or completed suicide), and the type of antidepressant investigated.[15–17]

One meta-analysis of randomized controlled trials (RCTs)[18] revealed weak evidence that SSRIs increased the risk of suicidal self-harm. However, for SSRIs, neither a beneficial nor a harmful effect on suicide deaths could be stated because they occur so rarely.[18] Another meta-analysis[16] showed that users of SSRIs had a 2-fold increase of fatal and nonfatal suicidal attempts. A recent meta-analysis (comparing the SSRI sertraline to placebo)[19] did not find any treatment effect on suicidal behavior, neither with regard to different age groups nor to different types of suicidal behavior. Likewise no differences in suicidal behavior were reported to be due to the various classes of antidepressants[15,16] with the exception of one study[20] that reported more deliberate self-harm with SSRIs than with tricyclic antidepressants (TCAs). A comprehensive analysis of the US Food and Drug Administration[11] reported that antidepressants (including SSRIs) pose only a small risk of inducing suicidal thoughts and suicide attempts in groups under 25 years of age; this risk decreased as age increased. A recent study[21] discussed that the antidepressants are even possibly protective for suicidal ideation in adults aged 25–64.

Meta-analyses of RCTs are assumed to be the gold standard for detecting causal relationships between the use of antidepressants and suicidal behavior. However, the included RCTs usually exclude suicidal patients, refer only to short periods of time, and are usually not designed to identify completed or attempted suicides.[22] Because the absolute number of patients attempting or committing suicide is very low, the failure to report a few cases can have a high impact.[23] Another disadvantage of meta-analyses is that data are pooled across different antidepressants, thus masking the risk profile of a single drug.

To obtain more precise information on the characteristics of the afflicted patients as well as on the development and precise nature of suicidality, it has been recommended that well-documented case reports be collected in addition to meta-analyses of RCTs and to pharmacoepidemiologic studies.[18] Case reports from the German spontaneous adverse drug reaction (ADR) reporting system have already been published.[24,25] In our study, a large data set from a European drug surveillance program (AMSP)[26] carried out in psychiatric hospitals in Germany, Austria, and Switzerland was analyzed. By allowing careful assessment of a series of single cases, this approach may help to detect risk factors and early signs of emergent antidepressant-induced suicidality. It should be stressed that our study is a heuristic approach, not a confirmatory test.

METHOD

The AMSP program for Drug Safety in Psychiatry (Arzneimittelsicherheit in der Psychiatrie) was established in 1993 as a continuous open-end study for the assessment of severe ADRs to all marketed psychotropic drugs during routine treatment of psychiatric inpatients. It currently includes 54 psychiatric institutions (15 university and 39 nonuniversity institutions, ie, 30 state hospitals and 9 psychiatric departments of general hospitals in Austria, Germany, and Switzerland). The AMSP replaces an earlier, similar drug surveillance program (Arzneimittelüberwachung in der Psychiatrie [AMÜP][27]).

The AMSP methods were described in detail earlier.[26,28] In brief, only clinically severe ADRs are assessed. The criteria of the program are based on the severity of the event itself and its potential danger to the patient's health. Adverse drug reactions are documented by trained psychiatrists, who contact the ward psychiatrists at regular intervals (at least every 2 weeks) and document the ADR cases in standardized questionnaires. Age, gender, and psychiatric and somatic diagnosis are recorded along with a detailed description of the adverse event, potential risk factors, clinical measures taken because of the ADR, and the subsequent outcome of the ADR. Psychiatric and somatic drug data (dosage, time course, concurrent medication), previous exposure to the imputed drugs, treatment after the adverse event, and outcome in case of rechallenge are also documented.

Probability rating: all these factors are taken into account in order to rate the probability of a causal relationship between medication and adverse event. The probability ratings are as follows: grade 1 = possible (ADR not known, time course or dosage unusual for drug in question, or alternative explanation for adverse event more probable), grade 2 = probable (ADR known for drug in question, time course and dosage in accordance with previous experience, and alternative explanation less probable), grade 3 = definite (in addition to criteria necessary for a "probable" rating, reappearance of the ADR after rechallenge with drug in question).

The cases are forwarded to the AMSP center at the psychiatric department of the University of Munich, reviewed by a senior member of the team, and then discussed at central case conferences attended by drug monitors from all centers, representatives of the German Federal Institute for Drugs and Medical Products (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft, AKdÄ) and drug safety experts from the pharmaceutical industry. After a consensus is reached and a probability rating is given to the adverse drug reaction, the completed case descriptions are sent to the various authorities as well as to the pharmaceutical companies involved. They are also stored in the central surveillance database for further analysis. Expert rating using the AMSP (and AMÜP) criteria was shown to be as reliable as the use of a formalized algorithm during the earlier AMÜP study.[29]

Data on drug use in all patients under AMSP surveillance at the participating centers are regularly documented by AMSP in order to estimate the frequency of an ADR occurring with a certain drug. On 2 reference days per year, all drugs and their dosages are recorded along with age, gender, and diagnoses. In addition, the participating centers provide the number of inpatients monitored per year as well as the mean duration of inpatient treatment for all monitored patients; both are broken down according to diagnostic groups.

AMSP assesses mainly ADRs occurring during inpatient treatment. In addition, ADRs leading to hospitalization are recorded. Both are explicitly documented.

Special Procedure of This Analysis

For this study, all cases of suicidal ideation or behavior judged to be related to antidepressants as an ADR were extracted from the database covering the period from 1993 to 2008 and were analyzed along with background information on demographic data and drug use in the patients under surveillance.

Criteria for assessing suicidality as an ADR: suicidality is a frequent illness-related feature of psychiatric inpatients. It is often difficult to differentiate between drug-related and illness-related events. The AMSP rates suicidality as an ADR only if it is connected with treatment-emergent symptoms that allow a judgment that the event is at least "possibly" drug related, eg, agitation, psychosis, unusual change in behavior, inner or motor restlessness. The unexpectedness of a suicidal action alone is not sufficient to rate it as drug-related. Special symptoms like emergent agitation have to be observed by the staff or reported by the patient. In particular, the assessment

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Table 1. Classification of Applied Antidepressant Medication (according to clinical convenience)

Classes of Antidepressant Medication	Substance
Monoamine oxidase inhibitors	Moclobemide Tranylcypromine
Noradrenergic and specific serotonergic antidepressant	Mirtazapine
Serotonin norepinephrine reuptake inhibitors	Duloxetine Venlafaxine
Selective serotonin reuptake inhibitors	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline
Tricyclic antidepressants	Amitriptyline Clomipramine Doxepin Imipramine Trimipramine
Other antidepressants	Bupropion Maprotiline Mianserin Nefazodone Reboxetine Trazodone

of ego-dystonic suicidal impulses, such as impulses experienced by the patients as strange to them, is relevant; it relies mostly on the explicit description by the patient concerned. For this reason, causality assessment is particularly difficult and often impossible in completed suicides, which are then rated as "unassessable." Such cases are not included in the present study.

While assigning probability ratings, researchers considered the possibility of an illness related event as an alternative cause in all cases of suicidal ADRs; however, dependent on the clinical features this was judged as less likely in the "probable" cases and as more likely in the "possible" cases. All cases of suicidal ADRs due to antidepressants were reassessed by the AMSP leader team including the heads of the regional and national AMSP groups in February 2009. These were discussed until a consensus was reached.

It would have been desirable to assess all cases of suicidal behavior irrespective of judgments on causality. However, due to the limited means of the AMSP, this was not feasible; even concerning completed suicides, only a few hospitals systematically document all of them.

Classification of Substances

Antidepressant drugs were classified according to clinical convenience (for details, see Table 1).

Data Evaluation

Data are presented as absolute numbers of ADRs and as incidence rates related to the number of patients exposed. The latter are estimated on the basis of data collected on the reference days per year from every hospital bed under surveillance and the absolute number of patients per year. Adverse drug reaction incidence rates are presented together with their confidence intervals. In view of the very low rate of serious side effects combined with the high number of patients exposed, confidence intervals are calculated according to the exact (asymmetric) method first described by Clopper and Pearson.[30] This method avoids the bias of the commonly used approximation methods (for a discussion of methods, see, eg, Engel et al[28]). Statistical inference is used as an exploratory technique, as the focus of the AMSP project is the descriptive presentation of ADR data, not the proof of hypotheses.

RESULTS

Demographic Characteristics and Data on Drug Use of Patients

The AMSP project surveyed a total of 311,374 patients at 85 hospitals between 1993 and 2008 (139,509 men and 171,865 women). Of these, 142,090 patients were treated with antidepressant medication (63.2% were women). There was no relevant difference in age, gender, and psychiatric diagnoses between patients taking antidepressants who had been surveyed by AMSP and those taking antidepressants who had exhibited suicidal ADRs (see Table 2).

A detailed overview of antidepressant subgroup drug use is given in Table 3. Approximately one-third (32%) of the patients with antidepressant medication were also treated with benzodiazepines.

Antidepressant use notably changed over time. Between 1993 and 2000, predominantly TCAs (51.2%) were given, whereas between 2001 and 2008, TCAs were administered less often (17.0%), and SSRIs (41.7%), noradrenergic and specific serotonergic antidepressants (NaSSAs) (30.2%), and serotonin norepinephrine reuptake inhibitors (SNRIs) (22.3%) predominated.

Details of Suicidal ADRs

From 1993 to 2008, 33 patient episodes of suicidality were observed, in which a relationship to antidepressant treatment was considered possible or probable. Fourteen of these cases occurred during the period 1993–2000 (53,042 antidepressant patients, 0.026%) and 19 during the period 2001–2008 (88,011 antidepressant patients, 0.022%).

They included 12 episodes of suicidal ideation, 18 suicide attempts, and 3 completed suicides (Table 4).

Fourteen events were assumed to have a probable, and 19 to have a possible, relationship to the drug (here: case-related, ie, 1 rating per case, Table 5).

Characteristics of Patients With Suicidal ADRs

The ages of the afflicted patients (male: n = 11; female: n = 22) ranged between 19 and 77 years. In the group under 26 years of age, there was 1 case with suicidal ADRs (ie, a relative frequency of 0.0011%). The group older than 25 years included the remaining 32 cases of suicidal ADRs (ie, a relative frequency of 0.024%). The majority of main diagnoses (22 patients) were affective disorders (*ICD-10*: F3; for an overview, see Table 2). Three patients had organic brain damage. Prior suicide attempts were known in 8 patients. Approximately half of the patients with suicidal ADRs

Table 2. Demographic Characteristics of Patients Who Developed ADRs in Comparison With All Surveyed Patients on Antidepressant Treatment

Characteristic	Suicidal Ideation (n = 12)	Suicide Attempt (n = 18)	Completed Suicide (n = 3)	All Patients With ADRs (n = 33)	All Patients With Antidepressant Medication (n = 142,090)
Age, y					
Average	44	51	68	50	49
Range	19–73	28–77	54–77	19–77	16–103
Gender, n					
Male	3	7	1	11 (33%)	52,354 (37%)
Female	9	11	2	22 (67%)	89,736 (63%)
Clinical history of prior SA, n	2	5	1	8 (24%)	unknown
Main diagnoses according to *ICD-10* [accessory diagnoses], n					
F1	1 [2]	0 [2]	0	1 [4] (3%)	5,526 (4%)
F2	0	2	0	2 (6%)	20,474 (14%)
F3	6 [2]	13	3	22 [2] (67%)	78,951 (56%)
F4 and F6	5 [7]	2 [1]	0	7 [8] (21%)	22,160 (16%)
Other	0	1	0	1 (3%)	13,141 (9%)

Abbreviations: ADRs = adverse drug reactions; *ICD-10* = *International Classification of Diseases, Tenth Revision*; SA = suicide attempt.

Table 3. Data on Drug Use Under Surveillance of the AMSP Between 1993 and 2008, Number of ADRs (suicidal ideation, suicide attempts, or committed suicides) [and Number of Suicidal ADRs in Which a Probable Relationship Was Assumed]

	Patients Monitored		All ADRs [ADRs With Probable Causal Relationship]	
Antidepressant Medication	n	Patients With Antidepressant Treatment, %	n	Patients With ADRs, %
All	142,090	100	33	100
MAOIs	3,436	2.4	2	6
NaSSAs	32,179	22.6	3	9
SNRIs	23,233	16.4	8 [3]	24
SSRIs	52,887	37.2	18[a] [10]	55
TCAs	41,052	29.0	1[a]	3
OADs	13,230	9.3	2 [1]	6
Antidepressants + benzodiazepines	45,521	32.0	15	45
Amitriptyline	10,721		1	
Bupropion	508		1	
Citalopram	14,682		8 [4]	
Clomipramine	5,155			
Doxepin	11,261			
Duloxetine	3,872		2 [1]	
Escitalopram	11,931		1 [1]	
Fluoxetine	4,074		1	
Fluvoxamine	3,549		2 [1]	
Imipramine	1,049			
Maprotiline	2,864			
Mianserin	2,477			
Mirtazapine	32,179		3	
Moclobemide	1,839		2	
Paroxetine	8,680		3 [2]	
Reboxetine	2,936		1 [1]	
Sertraline	10,067		3 [2]	
Trazodone	3,904			
Trimipramine	9,834			
Venlafaxine	19,401		6 [2]	

[a]Two or more drugs were imputed: 2 antidepressants (1 case), 1 antidepressant + 1 other drug (1 case), 1 antidepressant + 2 other drugs (1 case).

Abbreviations: ADRs = adverse drug reactions, AMSP = Arzneimittelsicherheit in der Psychiatrie, MAOIs = monoamine oxidase inhibitors, NaSSAs = noradrenergic and specific serotonergic antidepressants, OADs = other antidepressants, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

Table 4. Clinical Features in Connection With Suicidal Adverse Drug Reactions[a]

Type of Suicidality	No. of Cases	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis
Suicidal ideation	12	4	4	8	2
Suicide attempt	18	6	5	13	1
Completed suicide	3	…	…	2	…
All cases	33	10	9	23	3

[a]More than 1 feature per patient possible.

experienced the first manifestation of psychiatric illness, and about two-thirds were hospitalized for the first time.

Clinical Features During ADR

In the majority of patients (n = 23, 69.7%) suicidal ADRs were related to restlessness, 9 patients (27.2%) exhibited impulsiveness, and 3 (9.1%) developed a psychosis. Ten patients (30.3%) reported afterward that they had had an awkward ego-dystonia, ie, they had experienced suicidal impulses as strange to them (Table 4). Two of the patients who developed psychotic symptomatology had organic brain damage.

In comparison, within the cases of severe nonsuicidal psychic ADRs under antidepressant treatment (n = 215, toxic delirium not classified as psychic ADR), in 70 cases (ie, only in 32.6%), severe restlessness was recorded. For this symptom, the Fisher Exact Test comparing suicidal versus nonsuicidal ADRs was significant ($P < .001$). For psychosis (n = 42 in nonsuicidal psychic ADRs, 19.5%), no significant difference between suicidal and nonsuicidal psychic ADRs was found. Ego-dystonia and impulsiveness were not recorded as independent ADRs, ie, they were assessed only in the context of other psychic ADRs.

Medication

Selective serotonin reuptake inhibitors were involved in the majority of cases (n = 18); the causal relationship was considered to be probable in 10 episodes. Adverse drug

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Table 5. Medication and Likelihood of Causal Relationship With Respect to ADRs—All Cases [and Cases With Probable Relationship]

Type of Suicidality	No. of Cases	Medication			Co-Medication		Likelihood of Causal Relationship	
		SSRIs	SNRIs	All Other Antidepressants	Any Co-Medication	Benzodiazepines	Possible	Probable
Suicidal ideation	12	9[a] [5]	2 [2]	2[a] [1]	9	3	4	8
Suicide attempt	18	9 [5]	5 [1]	4 [0]	13	9	12	6
Completed suicide	3	0 [0]	1 [0]	2 [0]	3	3	3	0
All cases	33	18[a] [10]	8 [3]	8[a] [1]	25	15	19	14

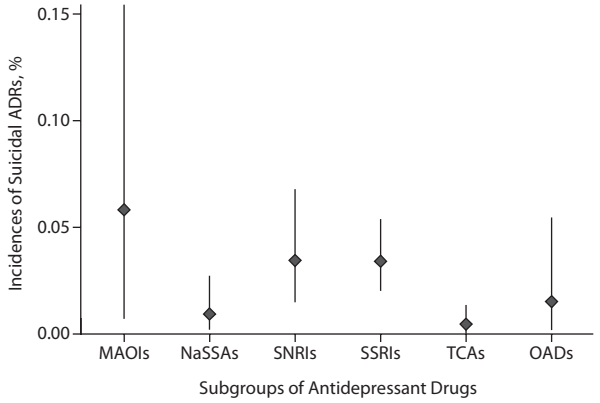
[a]Two or more drugs were imputed: 2 antidepressants (1 case), 1 antidepressant + 1 other drug (1 case), 1 antidepressant + 2 other drugs (1 case).
Abbreviations: ADRs = adverse drug reactions, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors.

Table 6. Dosages (high/medium/low) at the Onset of Suicidal Adverse Drug Reactions

Dosage	Substance Group, No. of Cases					
	MAOIs	NaSSAs	SNRIs	SSRIs	TCAs	OADs
High	0	0	3	2	0	1
Medium	2	2	3	14	1	0
Low	0	1	2	2	0	1

Abbreviations: MAOIs = monoamine oxidase inhibitors, NaSSAs = noradrenergic and specific serotonergic antidepressants, OADs = other antidepressants, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

Figure 1. Incidences[a] and Exact Asymmetric Confidence Intervals[b] for Suicidal ADRs Related to Subgroups of Antidepressant Drugs (possible and probable relationship)



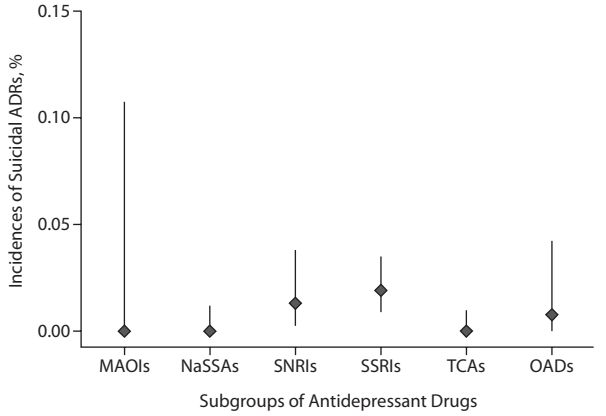
[a]Marked with a diamond.
[b]Marked by the line at both sides of the diamond.
Abbreviations: ADRs = adverse drug reactions, MAOIs = monoamine oxidase inhibitors, NaSSAs = noradrenergic and specific serotonergic antidepressants, OADs = other antidepressants, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

reactions were observed during treatment with SNRIs in 8 cases, 3 of which were considered to have a probable causal relationship (see Tables 3 and 5).

The dosages of antidepressants at the onset of ADRs were rated as low, medium, and high according to product information. Adverse drug reactions occurred with SSRIs mostly at medium dosages (in 14 out of 18 cases). For all other antidepressants, medium dosages were found as frequently as higher dosages (for details, see Table 6).

In one case, 2 antidepressants were considered to have caused the ADR (SI9, see Table 7); in another case, 1 antidepressant and 1 antipsychotic drug (SA18); and in a further

Figure 2. Incidences[a] and Exact Asymmetric Confidence Intervals[b] for ADRs Related to Subgroups of Antidepressant Drugs in Which the Likelihood of a Causal Relationship Between Drug and ADR Assumed to be Probable



[a]Marked with a diamond.
[b]Marked by the line at both sides of the diamond.
Abbreviations: ADRs = adverse drug reactions, MAOIs = monoamine oxidase inhibitors, NaSSAs = noradrenergic and specific serotonergic antidepressants, OADs = other antidepressants, SNRIs = serotonin norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

case, 1 antidepressant, 1 antipsychotic drug, and 1 benzodiazepine (S1). Monotherapy was administered in 8 cases (24%), and a probable causal relationship was considered in 4 of these cases (for details, see Table 7). In the total population of antidepressant patients, only 8.2% were on monotherapy.

At least 2 drugs in combination were administered in 25 cases. In 15 of these cases, benzodiazepines were given (see Tables 3 and 7). The numbers of cases of ADRs with the involved drugs and the corresponding data on drug use are shown in Table 3.

Most ADRs occurred shortly after onset of the imputed medication (12/33 cases within the first 7 days); in another 7 cases, the dosage of the imputed drug had been increased during the week before the ADR (for details, see Table 7).

Figure 1 shows all incidences of suicidal ADRs (possible and probable) for the antidepressant drug groups together with their asymmetric exact confidence intervals (SSRIs: incidence 0.034% [95% CI, 0.020–0.054]; SNRIs: 0.034% [95% CI, 0.015–0.068]; NaSSAs: 0.009% [95% CI, 0.002–0.027]; TCAs: 0.002% [95% CI, 0.000–0.014]). Figure 2 gives the results only for relationships rated as probable (SSRIs: 0.019% [95% CI, 0.009–0.035]; SNRIs: 0.013% [95% CI, 0.003–0.038];

Table 7a. Clinical Information on All Episodes of Suicidal Ideation That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (dosage during ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations	Subsequent Treatment, Special Notes Concerning Outcome[c]
SI1	73	M	F33.2		**Citalopram** ramipril bisoprolol acetylsalicylic acid atorvastatin diclofenac/ misoprostol	**20** 2.5 7.5 100 10 100	**1** 70 70 70 70 70	**2**	Sudden intrusive thoughts to jump out of the window	✓		✓		✕	4	1	Only moderate depression before ADR	Nortriptyline, melperone
SI2	19	F	F60.3		**Citalopram**	**20**	**11**	**2**	Inner and psychomotor restlessness with agitated alternate motion, possibly akathisia, increasingly unbearable → suicidality			✓		✕	2	1		Sertraline
SI3	49	F	F10.2	F41.0, F33.1	**Escitalopram** bisoprolol promethazine	**10** 2.5 25–100	**1** 30 6	**2**	Sudden inner tension and restlessness, agitation → suicidality (20 h after first intake)			✓		✕	15	2	Possible risk factor: preceding treatment with trimipramine (75–100 mg) withdrawn 5 d earlier → loss of sedative effect; but no such agitation on admission	Diazepam
SI4	51	M	F 32.2		**Paroxetine**	**60**	**2**	**2**	Increasingly intrusive, ego-dystonic thoughts (to hang himself, to stab himself in chest); increasing anxiety to give in to impulses; emergency hospitalization; in addition, burning skin sensation	✓	✓			✕	0	1	Risk factor: preceding treatment with mirtazapine (30 mg) withdrawn 3 d earlier → loss of sedative effect; however, no prior suicidality; high initial dosage of paroxetine	Improvement with dose decrease (to 30 mg) and additional lorazepam
SI5	40	F	F32.2		**Reboxetine** valproate lorazepam	**2** 1500 4	**1** 122 1	**2**	Immediately after reboxetine was given: inner restlessness, agitation, increasing after enhancement of dosage to 4 mg, additionally aggressiveness; at the same time, permanently low drive		✓	✓		✕	0	1		Lorazepam
SI6	50	F	F45.0	F41.2	**Sertraline** L-thyroxine theophylline	**150** 100 µg 250	**45 (37)** 400 400	**2**	Optical hallucinations, disordered consciousness, increasing paranoid thinking, ideation of being guilty, ego disturbances, thought broadcasting, feeling of disintegrating			✓	✓	✕	1	2	Risk factor: organic brain damage. Longer latency until ADR; for drug-induced psychosis, not unusual	Olanzapine
SI7	45	F	F33.2		**Venlafaxine** chlorprothixene diazepam mirtazapine	**75** 45 10 15	**1** 2 1 8	**2**	Inner restlessness, anxiety, strongly intrusive suicidal ideation and impulses			✓		✓	1	2	On admission, latent suicidal ideas, but clear-cut temporal relation of clinical deterioration to venlafaxine application	Mirtazapine (45 mg)

(continued)

Table 7a (continued). Clinical Information on All Episodes of Suicidal Ideation That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (dosage during ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations	Subsequent Treatment, Special Notes Concerning Outcome[c]
SI8	30	M	F42.0	F61.0	**Venlafaxine** lithium sulfate carbamazepine L-thyroxine	**225** 2310 800 25 µg	**31 (7)** 60 10 (5) 9	**2**	Increasing anxiety and intrusive ego-dystonic suicidality	✓				✗	u	3	Risk factors: organic brain damage; preceding treatment with perazine and lorazepam withdrawn 9 d earlier → loss of sedative effect, but no ego-dystonia, no suicidality on admission	Escitalopram. Increase of dosage of L-thyroxine shortly after ADR without exacerbation of suicidality
SI9	39	F	F32.9	F79	**Amitriptyline** **paroxetine** zolpidem	**50** **10** 10	**46** **5** 6	**1** **1**	Acoustic hallucinations (commenting and imperative voices that degrade her and tell her to kill herself)				✓	✗	3	1	Risk factors: organic brain damage; possible pharmacokinetic interaction: increase of plasma concentration of amitriptyline by paroxetine via inhibition of CYP2D6; previous episodes of acoustic hallucinations (only during the night and not as threatening)	Amitriptyline 50 mg continued, addition of haloperidol and lorazepam
SI10	53	F	F32.1	F43, F60	**Duloxetine** mirtazapine tramadol olanzapine lorazepam	**120** 15 150 10 1.25	**25 (4)** 29 29 28 (8) 23	**1**	Significant tenseness and inner restlessness. Patient was very agitated and pressed a ball extremely hard in her hand, because she felt like "exploding" → increasing suicidal ideation			✓		✓	1	1	In the past and later on several SAs without identifiable relationship to antidepressant treatment → restlessness, probable ADR, but suicidal ideation only possibly drug related	
SI11	33	M	F40.0	F31.1, F10.2	**Fluoxetine**	**40**	**47**	**1**	Intermittent restlessness, intrusive suicidal thoughts and impulses ("If I see an open window, I feel an urge to jump, although I don't want to")	✓	✓	✓		✗	9	5	During following episodes of abstinence, no restlessness or suicidality observed; no suicidality so far, but restlessness marked during earlier periods of abstinence	Citalopram
SI12	49	F	F45.0	F43.2, F17.2, F60.9, Z63	**Sertraline** gabapentin flurazepam acetylsalicylate simvastatin ibuprofen acetaminophen	**50** 1300 30 100 40 1200 500	**14 (8)** 30 (1) 36 30 30 2 4	**1**	Very sudden and surprising onset of suicidality		✓			✗	3	1	Acute psychosocial stress	Amitriptyline

[a]Bold font indicates the drug was imputed. [b]Likelihood of causal relationship: 1 = possible, 2 = probable. [c]Subsequent treatment: imputed drug was discontinued, if not explicitly mentioned otherwise; outcome: no further suicidality during treatment period, if not explicitly mentioned otherwise.

Abbreviations: ADR = adverse drug reaction, AMSP = Arzneimittelsicherheit in der Psychiatrie, F = female, M = male, SA = suicide attempt, u = unknown.

Symbols: ✓ = reported, ✗ = excluded, → = leading to.

Table 7b. Clinical Information on All Episodes of Suicide Attempts That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (dosage during ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations	Subsequent Treatment, Special Notes Concerning Outcome[c]
SA1	28	F	F32.9		**Citalopram** lorazepam	**20** 1	**41 (?)** 52	**2**	Sudden intrusive symptoms: depressive decompensation, suicidal thoughts, intention to run away, impulse to jump out of the window as if being pulled, feels like a marionette. No previous or subsequent similar experiences, considered completely unfamiliar	✓	✓			×	1	1	Late onset of ADR unusual, but no alternative explanation	During continuous treatment for 2 d ADR did not reappear. Patient refused further psychopharmacologic treatment due to ADR
SA2	58	F	F33.2	F84, F10.2	**Citalopram** metformin ramipril hydrochlorothiazide zolpidem	**20** 850 10 25 7.5	**4** 34 34 34 34	**2**	Increasing restlessness and intrusive thoughts about dying. SA: placed 2 hairdryers in bathtub. Patient commented afterward spontaneously: "That's not me having thoughts like that"	✓		✓		✓	36	1	Prior suicide attempt in adolescence after traumatic experience; no suicidal ideas for decades. Later paranoid-psychotic during amitriptyline, vulnerable to ADRs	Amitriptyline; committed suicide some months after dismissal
SA3	50	M	F33.1		**Duloxetine** quetiapine trimipramine	**120** 325 100	**55 (40)** 89 (30) 366	**2**	SA: patient was found unconscious after intake of trimipramine, quetiapine, and lorazepam. Later, patient described that he had experienced increasing restlessness since addition of duloxetine; patient was very tense, nervous, had prickling sensations; felt "like a light bulb switched on"			✓		✓	7	3	Narcissistic personality traits, close temporal relationship of restlessness and duloxetine administration; peculiar sensations that patient had never experienced before.	Venlafaxine, bupropion, quetiapine, lamotrigine
SA4	53	F	F32.1		**Fluvoxamine**	**100**	**46** (?; malcompliance in the first weeks)	**2**	Increasing agitation. SA: intake of 50 tablets of fluvoxamine (100 mg) and 4 tablets of midazolam and wine. Patient commented afterward: "It doesn't fit my personality. I can't track it anymore"	✓		✓		×	0	1	Psychosocial stress: death of husband 5 mo earlier, but no acute stress, no suicidal ideas so far	Mianserin

(continued)

Table 7b (continued). Clinical Information on All Episodes of Suicide Attempts That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (dosage during ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations	Subsequent Treatment, Special Notes Concerning Outcome[c]
SA5[d]	32	M	F42.0		**Paroxetine** promethazine lorazepam	**20** 150 3	**5** 7 6	**2**	Immediately after starting paroxetine, increasing restlessness and suicidality. On day 5, SA: suddenly jumped from partition wall to the sink. Experienced 2 lacerations on the head, injury to cervical spine. Patient commented afterward: "It suddenly occurred to me"		✓	✓		✗	10	1	Preexisting vague suicidal ideation, but no impulse to act upon it	Risperidone
SA6	62	F	F33.2		**Sertraline**	**50**	**4**	**2**	Immediately after starting sertraline inner restlessness, fiddling around, tormenting suicide impulses. SA: on day 3, intake of 20 tablets of sertraline. Called family members for help. Later, the patient reported she did not recognize herself, was very restless. No prior suicidal ideation	✓		✓		✗	1	1		Lorazepam, venlafaxine
SA7	42	F	F32.3		**Citalopram** lorazepam chloral hydrate	**40** 1 500	**28 (?)** 25 21	**1**	On treatment with citalopram, patient developed psychosis-like anxiety, ideas of guilt and self-accusations, disturbances of concentration and memory. SA: intake of 26 tablets of zopiclone				✓	✗	9	2	Prior outpatient treatment with amitriptyline was stopped because patient felt "strange." Alternative: psychotic depression, lack of effectiveness of antidepressant treatment	Citalopram continued, addition of haloperidol
SA8	46	F	F33.1	F61.0	**Citalopram** promethazine lorazepam brotizolam L-thyroxine captopril/ hydrochlorothiazide metoprolol	**60** 50 5 0.25 100 µg 25 100	**18 (2)** 220 220 220 220 220 220	**1**	SA: intake of unknown medication (3 times in 3 wk), leading to hospitalization. Family observed considerable restlessness prior to SA			✓		✗	4	2	No SA, but suicidal ideation frequent during course of illness in the past. On prior medication with clomipramine, no suicidality	No further information

(continued)

Table 7b (continued). Clinical Information on All Episodes of Suicide Attempts That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (dosage during ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations	Subsequent Treatment, Special Notes Concerning Outcome[c]
SA9	66	M	F32.1		**Citalopram** melperone	**20** 300	**5** 12	**1**	Severe inner restlessness after beginning citalopram. SA: tried to cut his arteries at the wrists with scissors. Afterward, patient described suicidal impulse as ego-dystonic	✓	✓	✓		×	u	2	Restlessness on admission. Preceding treatment with amitriptyline (150 mg) withdrawn 10 d before ADR → loss of sedative effect	Citalopram continued, addition of lorazepam
SA10	77	F	F32.2		**Citalopram** thioridazine lorazepam	**20** 6 1	**22** 35 –5	**1**	Increase of marked preexisting restlessness after onset of citalopram. Only transient improvement after addition of lorazepam. SA: harmed herself by jabbing a knife in the neck and wrist			✓		×	0	1	On admission severe agitation, intense self-accusations. Discontinuation of lorazepam 5 d before ADR	Mianserin, risperidone, lorazepam, sleep deprivation
SA11	44	F	F23.1		**Fluvoxamine** olanzapine	**100** 10	**4** 43	**1**	After onset of fluvoxamine increasing inner restlessness, sensation of inner heat, negative thinking, "I can't stand it anymore." Suicidal thoughts, psychomotor restlessness (rummaged around with documents). SA: intake of unknown tablets			✓		×	2	2	Acute psychosocial stress	Trimipramine
SA12	57	M	F32.2		**Mirtazapine**	**30**	**25**	**1**	SA: intake of tablets (unknown), strangulation, cutting of forearms, jumped off deer stand. Patient reported afterward that he had felt "blocked" and unable to do anything and therefore wanted to kill himself					×	u	1	Narcissistic traits; difficulty to accept depressive illness and acute psychosocial stress	Escitalopram, melperone
SA13	46	M	F33.1		**Mirtazapine** lorazepam	**15** 2.5	**1** 2	**1**	Massive agitation and restlessness immediately after first intake of mirtazapine. SA: harmed himself with a screwdriver and a piece of broken glass			✓		✓	26	22	Acute psychosocial stress. In youth, SA related to psychosocial stress	Lorazepam, venlafaxine, olanzapine

(continued)

Table 7b (continued). Clinical Information on All Episodes of Suicide Attempts That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (dosage during ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations	Subsequent Treatment, Special Notes Concerning Outcome[c]
SA14	64	M	F32.2		**Mirtazapine** zopiclone lorazepam piretanide/ramipril celecoxib	**45** 7.5 5–4 6 400	**9 (1)** 10 9 (1) 90 90	**1**	After onset of mirtazapine, restlessness and activation. SA: patient was found with a plastic bag pulled over his head and a string placed around his neck, no loss of consciousness			✓		✓	1	1	Minor reduction of benzodiazepines (lorazepam 5→ 4 mg), prior SA using a plastic bag led to admission	Mirtazapine continued, in addition diazepam
SA15	58	M	F32.3	F10.2, F13.2	**Moclobemide**	**300**	**5**	**1**	Restlessness after onset of moclobemide. SA: (1) placed himself on wet bedsheet, put disassembled coat-hanger in power outlet; (2) 1 d later: disassembled power outlet and cut electric wire with suicidal intention during increasing restlessness			✓		✓	0	3	Severe psychotic depression, lack of effectiveness of antidepressant. Preexisting suicidality; admission due to SA. Under rechallenge with moclobemide and additional haloperidol, again, restlessness and dysphoria, but no suicidal thoughts. Vanishing after withdrawal	Haloperidol
SA16	48	F	F43.2		**Venlafaxine**	**75**	**148**	**1**	SA: intake of tablets (unknown) and cut arteries at the wrist. Patient reported afterward: was surprising for herself, could not explain it	✓	✓			✗	0	1	Never suicidal ideation before, psychosocial stress exacerbated immediately before SA	No further psychopharmacologic treatment
SA17	38	F	F25.1		**Venlafaxine** olanzapine lorazepam	**375** 10 3	**51 (5)** 113 9	**1**	Preceding suicidal thoughts: while crossing a railway track, sudden impulse to throw herself in front of a train. SA: patient went to the attic, tried to strangle herself; stopped due to pain		✓			✗	22	1	No prior SA despite several episodes of severe depression. Venlafaxine for several weeks, but increase of dosage 5 d before SA	Venlafaxine continued; additional treatment with lithium
SA18	43	F	F 53.1		**Venlafaxine** **olanzapine** quetiapine biperiden lorazepam	**225** **5** 100 4 1	**8 (6)** **28** 28 40 29	**1** **1**	Restlessness in legs, rigidity prior to SA. SA: jumped off power pole, severe craniocerebral injury, multiple fractures			✓		✗	0	1	After delivery (2 mo before ADR), development of a postpartum psychosis with severe depressive symptoms and self-injuring behavior; twice in course of treatment, acute suicidality → transient transfer to closed ward. Possible akathisia, parkinsonoid	After SA treatment in medical hospital, further psychiatric treatment unknown

[a]Bold font indicates the drug was imputed. [b]Likelihood of causal relationship: 1 = possible, 2 = probable. [c]Subsequent treatment: imputed drug was discontinued, if not explicitly mentioned otherwise; outcome: no further suicidality during treatment period, if not explicitly mentioned otherwise. [d]Published case report (Göder et al[25]).

Abbreviations: ADR = adverse drug reaction, AMSP = Arzneimittelsicherheit in der Psychiatrie, F = female, M = male, SA = suicide attempt, u = unknown.

Symbols: ✓ = reported, ✗ = excluded, → = leading to.

Table 7c. Clinical Information on All Episodes of Completed Suicides That Were Reported and Rated as at Least Possibly Drug-Related ADRs During Surveillance of the AMSP Between 1993 and 2008[a]

Patient	Age, y	Gender	Psychiatric Diagnosis (*ICD-10*)	Accessory Psychiatric Diagnoses (*ICD-10*)	Medication	Daily Dosage at the Beginning of ADR, mg	Duration of Treatment Preceding ADR (duration of dosage at the beginning of ADR), d	Likelihood of Causal Relationship[b]	Clinical Features	Ego-Dystonia	Impulsiveness	Restlessness	Psychosis	Prior Suicide Attempt	Duration of Illness, y	No. of Hospitalizations	Special Risk Factors or Alternative Causes, Considerations
S1	77	M	F33.2		**Bupropion** **oxazepam** **levomepromazine** metoprolol/ hydrochlorothiazide acetylsalicylic acid digitoxin	**300** **140** **50** 47.5 100 0.07	**11 (5)** **45 (2)** **4** 12 12 12	**1** **1** **1**	Enhancing restlessness with increasing dosage of bupropion, leading to higher dosage of oxazepam and addition of levomepromazine. Jumped off a 10 m high bridge on the shore of a river. Several episodes of severe depression, but no suicidality before. Wife: "This is not like him"			✓		✗	4	8	Increasing restlessness after addition of levomepromazine possibly due to akathisia. Bupropion may have increased the plasma level of levomepromazine and vice versa. Alternatively, a possible paradoxical reaction to oxazepam
S2	73	F	F32.1		**Moclobemide** lorazepam amiloride/ hydrochlorothiazide	**300** 0.5 25	**11** 59 (35) 40	**1**	Prior to fatal event: depressive mood for years. Outpatient treatment with moclobemide for 3 weeks. Subsequently, agitation and SA (patient put wire around her neck) leading to hospitalization. Agitation on admission. Treatment without antidepressant, only lorazepam, improvement and discharge. General practitioner prescribed again moclobemide. Patient committed suicide 11 d later					✓	10	1	Of minor relevance: reduction of lorazepam (reduced from 3 mg 8 weeks before to 0.5 mg 4 weeks before ADR). Before completed suicide already agitation and SA during moclobemide exposure, chronic depression
S3	54	F	F31.4		**Venlafaxine** olanzapine lorazepam	**150** 5 0.75	**17 (14)** 10 17	**1**	Severe depression on admission. Amelioration of drive without significant amelioration of mood during treatment. Restlessness several days prior to ADR. Patient hanged herself			✓		✗	8	2	Additional risk factors: mamma carcinoma, mother committed suicide 1 y earlier, also during a hospitalization. Restlessness seen as ADR of venlafaxine, increasing before suicide

[a]Bold font indicates the drug was imputed. [b]Likelihood of causal relationship: 1 = possible.
Abbreviations: ADR = adverse drug reaction, AMSP = Arzneimittelsicherheit in der Psychiatrie, F = female, M = male, SA = suicide attempt, u = unknown.
Symbols: ✓ = reported, ✗ = excluded.

NaSSAs: 0.000% [95% CI, 0.000–0.011]; TCAs: 0.000% [95% CI, 0.000–0.009]). Both figures indicate a higher incidence of suicidal ADRs for SSRIs and SNRIs compared to NaSSAs and TCAs.

Only 1 patient used drugs from 2 antidepressive drug groups (SI9). For a pragmatic statistical treatment, we focused on those 32 patients who used only antidepressant substances categorized in 1 group of drugs and, accordingly, restricted the number of patients in the comparison group to those who used only antidepressive drugs from 1 of the groups. A simple 2-way table shows a significant imbalance of the drug groups, regardless of whether only the cases with a probable causal relationship (likelihood based $P = .003$) or all cases (likelihood based $P = .0001$) were considered. Selective serotonin reuptake inhibitors and SNRIs were more often imputed than TCAs and NaSSAs.

Table 7 gives detailed information on the individual cases, including clinical features, medication, causal relationship between ADRs and the drugs used, subsequent treatment, and outcome.

DISCUSSION

Thirty-three of the 142,090 patients taking antidepressant medication exhibited suicidal behavior as an ADR to antidepressants. Fourteen of these incidents were judged to be probably related to drug use. Restlessness was the most frequently observed clinical feature among the ADR symptoms in our cases. Furthermore, some patients explicitly reported impulsiveness and ego-dystonia. Only 8 of the 33 patients had a history of previous suicide attempts. Selective serotonin reuptake inhibitors and SNRIs were the most frequently imputed classes of antidepressant drugs.

In general, it is difficult to discriminate between suicidality as a symptom of the primary disorder and as a drug-induced event. Suicidality is known to be a complication of depression and is mentioned in the *ICD-10*[31] as well as in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[32] criteria. Thus, in general, one cannot assume a definite causal relationship between suicidal ADRs and drug treatment. In cases of completed suicide, it is even difficult to make a possible rating, since there is often a deficiency of information on the period immediately preceding the event, and it is no longer possible to ask the patient.

The analysis of ADRs in the international AMSP project is based on repeated and detailed assessments by experts, including the consideration of all clinical and differential diagnosis information.[26] The separation of probable from possible events is somewhat debatable as it has to rely more on subjective information than other areas of ADR assessment. Therefore, it is worth noting that the observed trends in relative frequencies of different AD groups are similar for all cases and those rated as probable.

The majority of our sample of patients with suicidal ADRs was women. This corresponds to the gender distribution of all inpatients treated with antidepressants in the AMSP project (in the analyzed period of 1993–2008). The distribution of diagnoses was also comparable. We were unable in our sample to investigate the association between the occurrence of ADRs and younger age, as was reported in the literature,[1,21,33] because the AMSP project includes only adult psychiatric inpatients (with a higher proportion of gerontopsychiatric patients). Our study observed only 1 case in the group under 26 years of age.

The notion that antidepressant drugs might facilitate suicidal events was discussed earlier, eg, within the AMÜP project, which preceded the AMSP project.[6] Enhancement of drive before ameliorating mood and also triggering of psychosis were considered possible risk factors for suicidality during treatment with first-generation antidepressant drugs.[6] These results referred mainly to activating TCAs. In the meantime predominantly sedative TCAs are used, due to the fact that SSRIs and SNRIs are preferred as drive-enhancing drugs.

Increased impulsiveness was first reported for fluoxetine,[3,34] and subsequently also for other SSRIs (for review see Healy et al[35]). Because SSRIs are administered to treat disorders with deficits of impulse control, this raises the issue of a paradoxical effect. Similarly, an enhancement and disinhibition of libido have been observed in single patients taking SSRIs,[36] whereas a loss of libido is considered a common adverse effect.

Motor restlessness, which resembles akathisia, was seen in several patients with suicidal ADRs in our study. SSRIs and other antidepressants have been reported to possibly trigger an akathisic state, thus increasing vulnerability to suicidality.[35] Moreover, akathisia has been considered a risk factor for suicidality.[3,24,37]

Suicidality was judged as an ADR only, if it was connected with relevant treatment-emergent symptoms. Severe restlessness occurred more frequently in connection with suicidal than with nonsuicidal psychic ADRs, which was not the case for psychosis. Comparisons of the frequency of the symptoms ego-dystonia and impulsiveness between suicidal and nonsuicidal psychic ADR cases were not analyzed here, since these symptoms have been assessed only in the context of other ADRs. To confirm a possible relation between the symptoms described (restlessness, ego-dystonia, impulsiveness) and suicidal ADRs, further investigations are necessary.

As regards current drug use, we observed suicidal ADRs mainly in patients taking SSRIs and SNRIs in our study. To the best of our knowledge, SNRIs have not yet been focused on in this context. The main imputed serotonergic medication (SSRIs, SNRIs) and the clinical features described (impulsiveness, inner and motor restlessness) suggests an involvement of the serotonergic system in suicidal ADRs.[38] However, other mechanisms may be also relevant; 1 case of suicidal ideation was observed with reboxetine (case number SI5).

The discrepancy between the results of our study and those of the RCTs or meta-analyses of RCTs is due to methodological differences. Random controlled trials on the one hand have in general the tendency to exclude patients with

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emergent suicidality. On the other hand, RCTs count all events of suicidality during antidepressant treatment irrespective of causality considerations whereas AMSP counts only cases with at least some evidence for the drug involvement. Furthermore, our study refers only to inpatients.

An inspection of the case reports revealed a larger proportion of monotherapy among patients with suicidal ADRs in comparison to the total population. In general, polypharmacy is a known risk factor for ADRs and was explicitly assumed, eg, in case SI9. It is striking that there was a higher proportion of co-medication with benzodiazepines in the suicidal ADR cases (15 of 33 cases, ie, 45% compared to 32% of the total population). Benzodiazepines are commonly prescribed with antidepressants (in almost one-third of all antidepressant patients) as can be seen in the data on drug use. It could be argued that benzodiazepines play a role in the disinhibition of impulses contributing to suicidal behavior. On the other hand, benzodiazepines may have been used in the treatment of more severely ill patients, who later developed suicidal ADRs. In contrast to the imputed antidepressants, benzodiazepines were successfully continued in most of the 15 cases and introduced for treatment of the ADR in other cases. In their assessment of single cases, the experts did not include benzodiazepines except in 1 case in which oxazepam was imputed (case number S1).

The results have to be interpreted with the AMSP method in mind. The outstanding advantage of this surveillance system is the detailed analysis of single cases. This allows precise assessment of all factors contributing to ADRs. Furthermore, the observed ADRs can be related to the rate of drug use in the participating centers. A general limitation of the method, however, is that ADRs are probably underreported, especially behavioral ADRs, which may go unrecognized. Another general problem in the analysis of ADRs is that the more frequent reports of ADRs in connection with newer substances may bias the findings. Furthermore, the increasing public debate on suicidality during treatment with SSRIs might influence awareness and lead to selective observation and reporting. However, in our study, no increase in the number of reports in the more recent observation period was found. We also registered suicidal ADRs during treatment with other drugs, eg, moclobemide and reboxetine.

The advantages and shortcomings of the AMSP approach have to be compared with those of other methods of ADR assessments such as controlled trials, cohort studies, or case control studies.[28] The AMSP method assumes a distinct position within drug surveillance systems due to the following features. It allows a detailed analysis of single cases, the possibility of relating observed ADRs to data on actual drug use, and the comparison of ADR data for different compounds within the same population.

CONCLUSION

The large data set of AMSP supports the view that antidepressant-triggered suicidality (primarily by SSRIs and SNRIs) is rare; however, it is a very serious ADR. It is important to be aware of suicidal ideation and behavior as an at least possible adverse reaction to antidepressant treatment. The following clinical symptoms were frequently observed in patients who have been judged to exhibit suicidal ADRs: restlessness, ego-dystonia, and/or impulsiveness. Whether there is an actual connection between these characteristics and suicidal ADRs should be examined in further studies.

Drug names: amiloride (Midamor and others), atorvastatin (Lipitor), biperiden (Akineton), bisoprolol (Zebeta and others), bupropion (Aplenzin, Wellbutrin, and others), captopril (Capoten and others), carbamazepine (Carbatrol, Equetro and others), celecoxib (Celebrex), citalopram (Celexa and others), clomipramine (Anafranil and others), diazepam (Diastat, Valium, and others), diclofenac (Flector, Zipsor, and others), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac, Sarafem, and others), flurazepam (Dalmane and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), hydrochlorothiazide (Microzide, Oretic, and others), ibuprofen (Caldolor, Ibu-Tab, and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lorazepam (Ativan and others), metformin (Riomet, Fortamet, and others), metoprolol (Toprol, Lopressor, and others), mirtazapine (Remeron and others), misoprostol (Cytotec and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), promethazine (Promethegan and others), quetiapine (Seroquel), ramipril (Altace and others), risperidone (Risperdal and others), sertraline (Zoloft and others), simvastatin (Zocor and others), theophylline (Elixophyllin, Theochron, and others), tramadol (Ultram, Ryzolt, and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), valproate (Depacon and others), venlafaxine (Effexor and others), zolpidem (Ambien, Zolpimist, and others).

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