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Suicidal Ideation and Suicidal Behavior as Rare Adverse Events of Antidepressant Medication: Current Report from the AMSP Multicenter Drug Safety Surveillance Project

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Abstract

Background: Suicidal ideations, suicide attempts, and fatal suicides are rare adverse drug reactions to antidepressant drugs, but they essentially are clinically relevant. Drawing on a larger dataset of the European drug surveillance program, the present naturalistic study updates a previous contribution (Stübner et al., 2010).

Methods: First an analysis of the comprehensive data collected in 81 psychiatric hospitals from 1993 to 2014 by the European drug surveillance program Arzneimittelsicherheit in der Psychiatrie was made. All documented single cases of suicidal ideations or behavior judged as adverse drug reactions to antidepressant drugs were carefully assessed as to their clinical features and drug prescriptions.

Results: Among 219,635 adult hospitalized patients taking antidepressant drugs under surveillance, 83 cases of suicidal adverse drug reactions occurred (0.04%): 44 cases of suicidal ideation, 34 attempted suicides, and 5 committed suicides were documented. Restlessness was present in 42 patients, ego-dystonic intrusive suicidal thoughts or urges in 39 patients, impulsiveness in 22 patients, and psychosis in 7 patients. Almost all adverse drug reactions occurred shortly after beginning antidepressant drug medication or increasing the dosage. Selective serotonin reuptake inhibitors caused a higher incidence of suicidal ideation and suicidal behavior as adverse drug reactions than noradrenergic and specific serotonergic antidepressants or tricyclic antidepressants, as did monotherapy consisting of one antidepressant drug, compared to combination treatments.

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Significance Statement

The debate on suicidal thoughts and behavior as adverse drug reactions of treatment with antidepressants is still ongoing. While pharmacoepidemiological studies indicate a decline in suicides with increasing prescriptions of antidepressants, meta-analyses of controlled trials and clinical reports suggest possible new-onset suicidality due to antidepressant treatment. A drug monitoring program identified 83 cases of suicidal adverse drug reactions that may be associated with antidepressant treatment. The analysis allows to describe clinical features that might be considered as possible warning signs. The results show that antidepressant-induced suicidal thoughts and behaviors are rare and that the risk of developing suicidal adverse drug reactions appears to be different for various groups of antidepressants. There was a higher proportion of antidepressant monotherapy among patients with suicidal adverse drug reaction compared with all patients monitored.

Conclusions: The study supports the view that antidepressant drug-triggered suicidal ideation and suicidal behavior (primarily with selective serotonin reuptake inhibitors) are rare. Special clinical features (restlessness, ego-dystonic thoughts or urges, impulsiveness) may be considered as possible warning signs. A combination therapy might be preferable to antidepressant drug monotherapy when beginning treatment.

Keywords: antidepressants, SSRI, adverse drug reaction, suicide, drug safety

Introduction

An essential goal of prescribing medication with antidepressants (ADs) is to prevent patients from attempting or committing suicide and to treat or avert suicidal ideation. In fact, pharmacoepidemiological studies have shown that suicides declined as the prescription rate of AD increased (Möller, 2006; Brent, 2016). However, since 1988, enlarged and new-onset suicidal activities have been reported in association with antidepressant medication, first with imipramine (Damluji and Ferguson, 1988), later with maprotiline (Rouillon et al., 1989) and fluoxetine (Teicher et al., 1990). Suicidal ideations were first described as adverse drug reactions (ADRs) to ADs in connection with psychomotor activation, especially ADs with low sedative effects (Grohmann et al., 1993; Ströbel et al., 1994). In some cases they have been a consequence of drug-induced psychosis (Grohmann et al., 1993). Over the last 2 decades, the controversy surrounding this issue has focused on the role of selective serotonin reuptake inhibitors (SSRIs) (Healy and Whitaker, 2003; Whittington et al., 2004, 2005; Juurlink et al., 2006; Möller et al., 2008).

Meta-analyses of randomized controlled trials (RCTs) have yielded contradictory results (Baldessarini et al., 2017). Gunnell and colleagues stated in their meta-analysis that the effects of SSRIs could not be assessed because of the rarity of suicidal events (Gunnell et al., 2005). Whereas one analysis of RCTs (Vanderburg et al., 2009) reported no effect on suicidal behavior, neither for different age groups nor different types of suicidal behavior, another review (Fergusson et al., 2005) described a 2-fold increase of fatal and nonfatal suicide attempts. A third study reported only weak evidence that SSRIs increased the risk of suicidal self-harm (Martinez et al., 2005). Another meta-analysis found only a small risk of inducing suicidal thoughts and suicide attempts in groups of patients under 25 years of age, and this risk decreased as age increased (Stone et al., 2009). The most recent meta-analysis on long-term RCTs of ADs found an increased rate of suicide attempts during long-term treatment with ADs. Nevertheless, the authors concluded that it is still unclear whether ADs increase the risk of suicide attempts (Braun et al., 2016).

In 2010 we reported data on 33 cases of suicidal ideation and suicidal behavior, which had been observed by the European drug surveillance program AMSP (Arzneimittelsicherheit in der Psychiatrie) and judged to be related to the administration of ADs (Stübner et al., 2010) over the time period of 1993 to 2008 (see also Baldessarini, 2011 and Stübner et al., 2011).

It was found (Stübner et al., 2010) that mainly the clinical features of restlessness, impulsiveness, and ego-dystonic thoughts or urges (i.e., patients experiencing suicidal thoughts and urges as strange to themselves) preceded drug-induced suicidal ideation and suicidal behavior or accompanied it, respectively. A higher incidence of suicidal ADRs was observed in patients who had received SSRIs or selective serotonin norepinephrine reuptake inhibitors (SNRIs) compared with patients receiving noradrenergic and specific serotonergic antidepressants (NaSSAs) or tricyclic antidepressants (TCAs). The present study is based on a larger database allowing more powerful analyses.

METHODS

Data from the AMSP program for Drug Safety in Psychiatry (Arzneimittelsicherheit in der Psychiatrie) collected from 1993 to 2008 had already been analyzed using the same methods (Stübner et al., 2010). Now a follow-up analysis was made (from the above-mentioned AMSP data collected from 1993 until 2014) to prove the previous findings reported on a small sample dataset drawn from the larger dataset.

The AMSP program was established in 1993. It was to be a continuous, open-end study for the assessment of severe ADRs to all marketed psychotropic drugs during routine treatment of psychiatric inpatients in Austria, Germany, and Switzerland. The AMSP thus replaced an earlier, similar drug surveillance program (Arzneimittelüberwachung in der Psychiatrie [AMÜP]; (Grohmann et al., 1993; Ströbel et al., 1994).

The AMSP methods were described in detail earlier (Engel et al., 2004; Grohmann et al., 2004; Grohmann et al., 2014). 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. ADRs are documented by trained psychiatrists who contact the ward psychiatrists and document the ADR cases using standardized questionnaires. Age, gender, and psychiatric and somatic diagnoses are recorded along with a detailed description of the adverse event, potential risk factors, clinical measures taken because of the ADR, and its subsequent outcome. The psychiatric and somatic

drug data (dosage, time course, concurrent medication), previous exposure to the imputed drugs, that is, drugs that have been evaluated as the suspected cause of adverse reactionstreatment after the adverse event, and outcome in case of rechallenge are also documented.

All these factors are taken into account to rate the probability that a causal relationship between medication and adverse event is possible, probable, or definite according to AMSP criteria. After careful discussion at case conferences, the cases are stored in the central surveillance database for further analysis.

Data on drug use by all patients under AMSP surveillance at the participating centers are regularly documented on 2 reference days per year. All drugs and their dosages are recorded along with age, gender, and diagnoses of the patients.

Special Procedure of this Analysis

For the present study, all cases of suicidal ideation or behavior, which were judged to be possibly or probably causally related to ADs and thus assessed to be ADRs, were extracted from the database covering the period from 1993 to 2014. They were then analyzed along with background information on demographic data and drug use of the patients under surveillance.

Criteria for Assessing Suicidal Ideation or Behavior as an ADR

Suicidal thoughts and attempts are frequently illness-related features of psychiatric inpatients, and it is often difficult to differentiate between drug-related and illness-related events. As the course of psychiatric illness itself can never be completely excluded as a contributing factor, a "definite" causal relationship between the ADR and the drug cannot be assumed. However, in our assessment system, suicidal ideation or behavior is rated as an ADR only if it is connected with treatment-emergent symptoms. This allows us to judge whether the event is at least "possibly" drug related, for example, inner or motor restlessness, agitation, ego-dystonic thoughts or urges, psychosis, or change in behavior. The unexpectedness of a suicidal action alone is not sufficient to rate it as a drug-related event. Special symptoms like emergent agitation have to be observed by the staff or reported by the patient. In particular, the assessment of ego-dystonic, suicidal impulses such as urges and thoughts experienced by the patients as completely strange to themselves are relevant and rely mostly on the concerned patient's explicit description. For this reason, it is particularly difficult and often impossible to assess causality in fatal suicides, which are then rated as "not assessable." Such cases are not included in the present study.

Classification of Substances

ADs were classified according to clinical conventions: as monoamine oxidase inhibitors (MAOIs), NaSSAs, SSNRIs, SSRIs, or TCAs. The following substances were subsumed under "other antidepressants" (OADs): bupropion, nefazodone, reboxetine, tianeptine, trazodone.

Data Evaluation

ADRs are represented in absolute numbers and incidence rates. The number of patients exposed to a drug (or drug group) was estimated on the basis of drug-use data collected on 2 reference days per year. ADR incidence rates are presented together with exact confidence intervals (Clopper and Pearson, 1934).

The effects of age, gender, diagnosis, and drugs on suicidal ADRs were evaluated statistically by chi-squared or Fisher's exact tests. However, statistical inference was used as an exploratory technique, since the focus of the AMSP project is the descriptive presentation of ADR data, not the proof of hypotheses.

Evaluations based on the AMSP data bank have been approved by the Ethics Committee of the University of Munich. This study adhered to the Declaration of Helsinki and its later amendments

RESULTS

Demographic Characteristics and Data on Drug Use of Patients

Between 1993 and 2014, a survey was made of 447,566 patients receiving psychopharmacological treatment. Of these, 219,635 patients were treated with ADs.

The use of ADs changed fundamentally over time (see supplementary Fig. S1). In 1994, 76% of the patients treated with ADs received TCAs. In 2000, more patients were treated with SSRIs (37%) than with TCAs (34%), and SSRIs remained from then on the subgroup most often applied, although their usage has somewhat declined. From 2002 onwards, NaSSAs were administered in about 27%. In 2014, SSRIs were the ADs most often administered (38%), followed by SNRIs (32%), NaSSAs (26%), and TCAs (11%). MAOIs (about 1%) were used in only rare cases. In 2014, OADs were applied in about 20%.

A total of 83 cases of suicidal ADRs were documented during the period 1993 to 2014: 44 cases of suicidal ideation, 34 attempted suicides, and 5 fatal suicides. We analyzed the possible influences of demographic characteristics on the incidence rates of suicidal ADRs. While gender did not seem to have an effect, an impact was found for age and diagnosis: suicidal ADRs were more often seen in patients younger than 30 years (compared with their share in the AMDP dataset) and less often in patients older than 60 years. Suicidal ADRs were also more often seen in diagnoses of affective disorders (ICD 10: F3) and less often in diagnoses of schizophrenia and related disorders (ICD 10: F2; Table 1).

Clinical Features During ADRs and Details of Suicidal ADRs

From 1993 to 2014 suicidal ADRs were related to restlessness (52%), ego-dystonic thoughts or urges (47%), and impulsiveness (27%) in the majority of patients; few patients suffered from psychosis (8%; more than one feature per patient possible).

Time of Onset

Most suicidal ADRs occurred shortly after beginning AD medication or increasing the dosage. Fifty-nine of the 83 ADR cases occurred within the first 7 days (71%), 18 cases between day 7 and 14 (22%), and only 6 afterwards (2 had psychoses: 7%).

Subsequent Treatment and Outcome

Several treatment strategies were applied. In most of the cases, the imputed drugs were discontinued (n = 66, i.e., 79.5%); dosage was reduced in another 5 cases (6%). In 22 cases (26.5%) a transfer to a ward or institution with more intensive care or another hospital was necessary. Additional drugs to counteract the ADR were administered in 34 cases (41%, mostly benzodiazepines); in

Table 1. Demographic Characteristics of Patients Who Developed Suicidal ADRs in Comparison with All Patients on Antidepressant Treatment under Surveillance of the AMSP Project

Characteristic	Patients with Antidepressant Treatment		Patients with Suicidal ADRs		Significance Tests (ML-χ^2)
	n	%	n	%	
	219,635	100	83	100	
Age [years]					$\chi^2=10.79$, $P=.005$
<30	29,359	13.4	18	21.7(+)	
30–60	124,939	56.9	52	62.6	
>60	65,337	29.7	13	15.7(-)	
Gender					$\chi^2=1.15$
Male	82,605	37.6	36	43.4	$P=.28$
Female	137,030	62.4	47	56.6	
Main diagnosis according to ICD10					$\chi^2=12.62$ $P=.013$
F1	9,486	4.3	2	2.4	
F2	28,889	13.2	4	4.8(-)	
F3	128,930	58.7	58	69.9(+)	
F4 and F6	32,808	14.9	16	19.3	
Other	19,522	8.9	3	3.6	

Abbreviations: ADR, adverse drug reactions; AMSP, Arzneimittelsicherheit in der Psychiatrie; ICD-10, International Classification of Diseases, Tenth Revision; ML-χ^2, maximum-likelihood chi-square tests.

33 cases nonpharmacological interventions were used (mostly psychotherapy).

Imputed Medication

The observed numbers of ADRs during treatment with ADs were compared to all patients monitored while taking the imputed medication in the period 1993–2014.

Table 2 gives a detailed overview of the AD subgroup and single-drug use of the patients with suicidal ADRs compared with all other patients surveyed by AMSP together with the results of the descriptive Fisher's exact test. SSRIs were involved in the majority of the ADR cases (n=47, i.e., 57%). Patients with suicidal ADRs were more often treated with SSRIs compared with all patients on ADs (57% vs 38%) and less often with NaSSAs (10% vs 26%) or with TCAs (4% vs 24%). The differences were statistically significant for SSRIs, NaSSAs, and TCAs and also for the single substances citalopram and mirtazapine.

In 71 cases a single substance was considered to have caused the ADRs; in another 4 cases AD combinations were imputed. In 8 cases a combination of at least 1 AD and another drug was regarded as having provoked the ADRs: in 5 cases an antipsychotic drug, in the other 3 cases a tranquillizer or methylphenidate.

Figure 1 shows the relative frequencies of suicidal ADRs for the different subgroups of ADs together with their exact confidence intervals. Only those cases were included in which a single AD had been imputed for the ADR (n=71). Higher rates were observed for SSRIs compared with NASSAs and TCAs (for details, see the legend to Figure 1).

The median AD dosages of the ADR patients at the onset of ADRs were similar or even lower than that of the total population.

AD monotherapy (1 AD without any psychotropic comedication) was administered in 27 of the 83 ADR cases (33%), mostly SSRIs (n=14; most often citalopram, n=7). Only 16% of the total population of AD patients was on AD monotherapy. The difference was significant (see Figure 2). Furthermore, the part of combinations of AD with tranquillizer (benzodiazepines) without any other psychotropic drugs was higher in the ADR group (13% and 6%, respectively). In contrast, the combination of AD with antipsychotics (APs) was seen less often in the ADR group (12% vs 22%). Polypharmacy, that is, combinations of ADs with more than one additional group of psychotropic drugs, was also lower in the ADR patients (33% vs 47%).

These results were in accordance with the findings of a case/noncase analysis comparing the 83 cases of suicidal ADRs with 4294 cases of nonsuicidal ADRs in AD treated patients ("noncases", see supplementary Material). The reported odds ratios (ROR) concerning the occurrence of suicidal ADRs were significantly higher than 1 in the ADR group for AD monotherapy (ROR=2.9; CI1.80–4.60) and for the combination of AD plus TR (ROR=2.7; CI 1.41–5.16) and significantly lower than 1 for AD plus APs (ROR=0.4; CI 0.20–0.77) as well as for polypharmacy (i.e., AD plus more than one additional group of psychotropic drugs; ROR=0.6; CI 0.36–0.91; see supplementary Table 1). The time-to-onset of ADR was not significant different for suicidal and nonsuicidal ADRs (median: 8.5 days vs 9 days in noncases, see supplementary Material; supplementary Table 2; supplementary Figure 2).

Discussion

The results show that suicidal ADRs, that is, suicidal ideations, suicide attempts, and fatal suicides, can occur in patients treated with ADs, but these events are rare. Restlessness and ego-dystonic thoughts or urges were the most frequently observed clinical features accompanying the ADRs, followed by impulsiveness. SSRIs were responsible for the highest rates of these ADRs, whereas TCAs and NaSSAs were imputed very rarely. Monotherapy with one AD was significantly more common in ADR patients, whereas combinations of ADs and APs as well as polypharmacy were less frequently administered in ADR patients than in all AD patients.

Overall, from 1993 to 2014 in the AMSP project, suicidal ADRs were assessed in 83 of 219,635 patients treated with ADs. This is equivalent to an incidence rate of 0.04% (in detail: 44 cases

Table 2. Data on Drug Use under Surveillance of the AMSP and Number of ADRs Observed between 1993 and 2014

Antidepressant Subgroup or Substance	Patients with Antidepressant Treatment		Patients with Suicidal ADRs*		Fisher's Exact Test**
	n	%	n	%	P
All ADs	219,635[a]	100	83[b]	100	
MAOIs	4421	2.0	2	2.3	.68
NaSSAs	56,910	25.9	8	9.6	.0004
SNRIs	49,216	22.4	16	19.3	.60
SSRIs	83,457	38.0	47	56.6	.0006
TCAs	52,442	23,9	3	3.6	.000001
OADs	19,705	9.0	11	13.25	.18
Moclobemide	2294	1.0	2	2.4	
Mirtazapine	54,122	24.6	8	9.6	.0008
Duloxetine	12,059	5.5	3	3.6	.63
Venlafaxine	36,655	16.7	13	15.7	.88
Citalopram	23,664	10,8	22	26.5	.00005
Escitalopram	22,645	10.3	5	6.0	.28
Fluoxetine	5376	2.4	4	4.8	.15
Fluvoxamine	4078	1.9	2	2.4	.67
Paroxetine	9.988	4.5	5	6.0	.43
Sertraline	17,913	8.2	9	10.8	.32
Amitriptyline	13,405	6.1	3	3.6	.49
Agomelatine	3242	1.5	3	3.6	
Bupropione	3385	1.5	4	4.8	
Reboxetine	3266	1.5	1	1.2	
Tianeptine	112	0.1	1	1.2	
Trazodone	9797	4.5	2	2.4	.59

Abbreviations: AD, antidepressant; ADR, adverse drug reaction; AMSP, Arzneimittelsicherheit in der Psychiatrie; MAOI, monoamine oxidase inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant; OAD, other antidepressant.

* Imputed drugs for suicidal ADRs.

** Descriptive Fisher's exact tests were performed if at least 4000 patients were monitored while on a drug.

[a] Treatment with more than one antidepressant possible.

[b] In 4 cases, 2 antidepressants were considered to have caused the ADR.

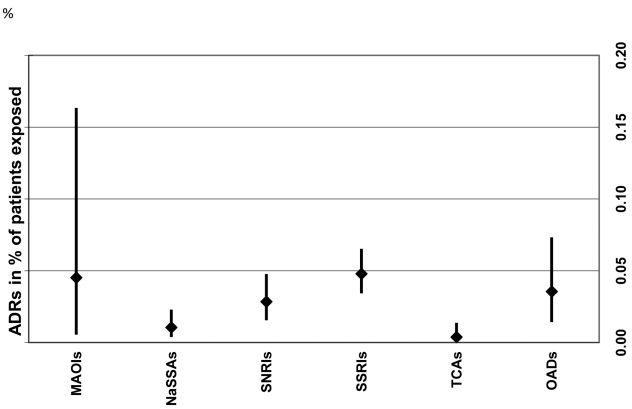

Figure 1. Incidences (diamonds) and exact asymmetric Cis (diamond with lines) for suicidal ADRs related to subgroups of antidepressant drugs (cases in which only a single antidepressant (AD) was assumed to cause the ADR; n=71). Serotonin reuptake inhibitors (SSRIs), n=40: incidence 0.05%; 95% CI between 0.034 and 0.07; serotonin norepinephrine reuptake inhibitors (SNRIs), n=14: 0.03% [95% CI, 0.016–0.05]; monoamine oxidase inhibitors (MAOIs), n=2: 0.05% [95% CI, 0.005–0.16]; noradrenergic and specific serotonergic antidepressants (NaSSAs), n=6: 0.01% [95% CI, 0.004–0.02]; tricyclic antidepressants (TCAs), n=2: 0.00% [95% CI, 0.000–0.01]; other antidepressants (OADs), n=7: 0.04 [95% CI, 0.014.–0.07].

of suicidal ideation, 34 attempted suicides, and 5 committed suicides). This finding does not agree with certain epidemiological data showing a higher percentage of suicidal ideation, as outlined by Baldessarini (2011). The apparent discrepancy is probably mainly due to different methodological approaches. Thus, in our study "cases" are recorded only when suicidal ideation or behavior is judged to be related to a particular antidepressant medication and additional symptoms allowing such a judgement are present (see Stübner et al., 2011).

In the period between 2009 and 2014, we found suicidal ideation and suicidal behavior to be an ADR in 0.065% of AD patients (50 cases of 77,545 AD patients); in the previously analyzed period between 1993 and 2008, they occurred in 0.023% (Stübner et al., 2010). This increase may be attributed to the ascending use of SSRIs and a greater awareness within the AMSP surveillance project resulting from our earlier report on suicidality as a rare ADR of ADs (Stübner et al., 2010).

It is important to note that the suicidal ADRs occurred within the first week (in 71% of the cases) or the first 2 weeks (93%) after onset or dosage increase of the imputed AD. This indicates that attention should be paid to possible suicidal ideation and behavior especially at the beginning of AD therapy. Our findings are in agreement with the data of Coupland and colleagues, who reported increased rates of suicides and attempted suicides or self-harm by persons with depression in the first 28 days of starting or stopping antidepressants; they also emphasized the need for careful monitoring of patients during these periods (Coupland et al., 2015).

Other factors might be correlated with an increased risk of developing suicidal ideation or behavior. However, we were unable to make a systematic analysis to identify such possible factors using our database.

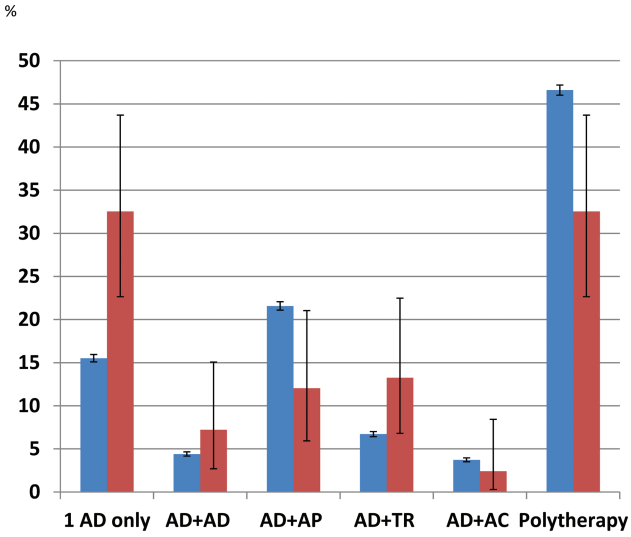

Figure 2. Mono- and combination treatments in percent of all patients with antidepressant treatment monitored by Arzneimittelsicherheit in der Psychiatrie (AMSP; in blue, left bars) and in percent of all patients with suicidal adverse drug reactions (ADRs; in red, right bars), with CIs. AC, anticonvulsant; AP, antipsychotic drug; TR, tranquillizer.

Three clinical features could be identified as possible warning signs of emerging drug-induced suicidal ideation or suicidal behavior: restlessness, ego-dystonic thoughts or urges, and increased impulsiveness. These symptoms are similar to the "activation syndrome" as described by the Food and Drug Administration as a risk factor of suicidal ADR induced by ADs in some patients. The syndrome includes anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania (Culpepper et al., 2004).

Restlessness was the most frequent clinical feature during the entire period from 1993 to 2014 (52%). Motor restlessness resembles akathisia, which has been considered a risk factor for attempting suicide (Teicher et al., 1990; Arzneimittelkommission der deutschen Ärzteschaft, 2004; Seemüller et al., 2009). SSRIs and other antidepressants have been reported to possibly trigger akathisia, thus increasing vulnerability to eventually fatal suicidal (Healy et al., 1999).

Ego-dystonic thoughts or urges, that is, suicidal thoughts or behavior appearing strange to the inflicted patients themselves, were assessed in 47% of the patients with suicidal ADRs. It seems to be a rather specific clinical feature preceding suicidal ADRs. It shows similarities with obsessions in obsessive-compulsive disorders, which are usually treated with SSRIs. This raises the question of a possible paradoxical effect. Compared with our analysis of a smaller dataset earlier (Stübner et al., 2010), the present study registered ego-dystonic thoughts or urges more often. This effect might be explained by a greater awareness of this phenomenon as a consequence of our first study.

Increased impulsiveness—observed in 27% of our ADR patients–was first reported for fluoxetine (Teicher et al., 1990; Gualtieri, 1991) and subsequently also for other SSRIs (for review, see Healy et al., 1999). Since SSRIs are also administered to treat disorders with deficits of impulse control, this again raises the issue of a paradoxical effect. Similarly, an enhancement (Gelman and Atrio, 2017) and egodystonic disinhibition of libido have been observed in single patients on SSRIs (Greil et al., 2001), although loss of libido is considered a common adverse effect.

We observed suicidal ADRs mainly in patients on SSRIs (in 57% of our cases, most often citalopram). The involvement of serotonergic medication (SSRIs and SNRIs in 76% of cases) and the clinical features described (impulsiveness, inner and motor restlessness) may indicate an involvement of serotonergic mechanisms in triggering suicidal ADRs (Meyer et al., 2003). In contrast, the NaSSA mirtazapine was associated with a distinctly lower incidence of suicidal ADRs (in 10% of the ADR cases) in accordance with a pooled meta-analysis of the placebo control studies with mirtazapine (Kasper et al., 2010) as well as TCAs, which were involved in only 3.6% of suicidal ADRs. On the other hand, mirtazapine showed a propensity to trigger suicide attempts or self-harm in a large epidemiological study (Coupland et al., 2015).

Monotherapy (i.e., one AD without any psychotropic comedication) was more often found in the ADR group than in all AD patients as already described in our previous analysis (Stübner et al., 2010). Polypharmacotherapy is commonly considered a risk factor for ADRs, but it is often required in clinically severe cases. The ADs applied in monotherapy in our study were usually SSRIs (mainly citalopram) and SNRIs. These drugs in particular may increase the risk of suicidal ADRs when given without sedative comedications (note, 2 cases of monotherapy were with the NaSSA mirtazapine).

Courtet and López-Castroman (2017) proposed further investigation of the combination of antipsychotics with antidepressants regarding suicidal adverse reactions. In our study, AD and AP combination as well as polypharmacy are related to a lower incidence in ADR patients compared with the total group of patients treated with ADs. One could speculate that this difference might indicate that this combination has a suicide-preventing effect, possibly due to the sedative effects of the antipsychotics applied as comedication (usually quetiapine, olanzapine, and promethazine) and/or a serotonin antagonistic effect. An argument for the latter could be the fact that benzodiazepines seem to be not protective according to the results of this study.

The overall frequency of comedication of ADs with benzodiazepines (without any other psychotropic drugs) was higher in ADR patients than in all patients treated with ADs. However, benzodiazepines were used in almost one-half of the ADR patients (41%) to counteract the suicidal ADRs.

Comparing the 83 cases of suicidal ADRs with the cases of nonsuicidal ADRs in AD-treated patients in a case control analysis, these results could be confirmed (see supplementary Material). The ROR were significantly higher than 1 for AD monotherapy and for AD-TR combinations and lower for AD-AP combinations and for polypharmacy. Since underreporting is present in reporting of all ADRs, the influence of underreporting on the results may be reduced using this approach. Monotherapy of AD may be more frequent in the beginning of hospitalization. The time to onset of suicidal and nonsuicidal ADRs being similar indicates that the apparent "pro-suicidal" effect of AD monotherapy (McElroy et al., 2006; Mihanović et al., 2010) seems to be independent of the time to onset of suicidal ADRs, which is usually within 2 weeks.

The results have to be interpreted with the AMSP method and its strengths and limitations in mind (see also Stübner et al., 2010). The advantage of the surveillance system is that the single cases of ADRs can be analyzed very precisely. This allows assessment of all factors contributing to ADRs. Furthermore, the drugs applied in the observed ADRs can be related to the use of drugs in the centers participating in the AMSP project. A general limitation of the method, however, is that ADRs are often underreported. Another general problem is selective reporting of ADRs, especially when newer substances are involved. In this particular analysis, it should be noted that with regard to mental symptoms (as suicidal thoughts or behavior), it remains difficult to distinguish

between drug-related and illness-related events, even when all care is taken for the evaluation. Since the medication was not randomly assigned in this drug safety program in clinical routine, the choice of a particular antidepressant by the attending physician could have an impact. It might be that some antidepressants, for example, SSRIs, were preferred in patients prone to suicidality due to low toxicity. This bias cannot be ruled out. More accurate information could be gained in future research by case control designs that include no treatment and other treatment groups. In this study, we additionally applied a special form of case control design, the case/noncase approach, to confirm the results with another method (see supplementary Material). Finally, the public debate on suicidality during treatment with SSRIs (Baldessarini et al., 2017; Courtet and López-Castroman, 2017; Silverman, 2017) might have influenced the general awareness and led to selective observation and reporting in more recent years.

Conclusions

Our analysis of the large dataset of AMSP supports the view that suicidal ADRs can be triggered by AD treatment (primarily SSRIs) in rare cases. The results obtained previously are supported by the now larger database. Restlessness, ego-dystonic thoughts or urges, and impulsiveness are important clinical characteristics of patients who developed suicidal ideation or behavior as ADRs and may be considered possible warning signs. Especially in the first 2 weeks of antidepressant medication, special attention should be paid to these patients.

As regards suicidal thoughts or behavior as ADR, the results could indicate that a combination therapy might be preferable to AD monotherapy when beginning treatment. In particular, a co-medication with antipsychotics might be helpful to avoid the onset of suicidal ADRs. According to the present study, the very low risk of the AD-induced ADR of suicidal ideation and behavior does not seem to be reduced effectively by the combination of ADs with benzodiazepines alone, that is, without any other psychotropic drugs.

Supplementary Materials

Supplementary data are available at *The International Journal of Neuropsychopharmacology* online.

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