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ORIGINAL ARTICLE

Frequency of different anti-depressants associated with suicides and drug deaths

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Abstract From each case of suicide and drug-related death autopsied in the Institute of Forensic Medicine, Munich during the years 2001–2005, a toxicological investigation on anti-depressants (AD) was performed. In 180 suicides and 72 narcotic drug death cases, ADs were detected: 4 different classic tricyclic anti-depressants (TCAs), 6 other non-selective monoamine re-uptake inhibitors (NSMRIs), 5 selective serotonin re-uptake inhibitors (SSRIs) and 3 other ADs. The suicides were grouped further according to the type of suicide (violent or non-violent). The prescription frequency of the ADs in Germany, expressed as the defined daily dosages (DDDs), during the investigated years served for comparison. There were serious differences in the frequency of different ADs regarding to the manner of suicide. In cases associated with doxepin and trimipramine, non-violent suicides were distinctly over-represented, as in cases in which the drug itself was responsible for the death as in cases of non-violent suicides in other manners. In contrast, in cases with citalopram or opipramol, violent forms of suicides were significantly over-represented. For amitriptyline, the ratio was approximately balanced. For the remainder of the ADs, the case numbers were too low for a valid evaluation. The different frequency distributions of the ADs, associated with violent and non-violent suicides may be explained by their different pharmacological active profiles and the different lethality of overdoses of the different ADs. There was no indication at all for a special suicidal problem of SSRIs in juveniles. Amongst 1,127 suicides within 5 years, in an area with approximately 5 million people, the youngest suicide victim with SSRIs was 28 years old. In drug death cases, citalopram was obviously over-represented.

Keywords Anti-depressants · Suicide · Drug-related death · Frequency · Autopsy · Juveniles

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Introduction

In general, depression increases the risk for suicide [1, 2]. Classic hypnotics, suitable for suicide, like most barbiturates or bromo-urea derivatives, have been phased out long ago in Germany. In most cases, benzodiazepines are not suitable for suicide, at least not alone. Therefore, anti-depressants (ADs) remained as one of the last few groups of drugs, which are easily accessible for a depressive person and suitable for committing suicide. An overdose of ADs has a strong cardiotoxic effect [3]. In the years 2001–2005, the prescription of ADs has markedly changed in Germany. Whilst the number of defined daily doses (DDDs, the assumed average maintenance dose per day for a drug used for its main indication in adults) [4] of tricyclic anti-depressants (TCAs), which are prescribed in Germany, stayed almost constant, the prescription of the new selective serotonin re-uptake inhibitors (SSRIs) has rapidly increased (Fig. 1) [5–9]. For the first time in 2004, the SSRIs have overtaken the classic TCAs in the number of DDDs prescribed per year [7]. From the toxicological view, this switch is most welcome. The cardiotoxic potency of SSRIs is reported to be lower than that of TCAs [10–13]. On the other hand, SSRIs are suspected to increase the suicidality of depressive patients, especially of juveniles, but also of elder adults [14–26]. It was pointed out that acute akathisia

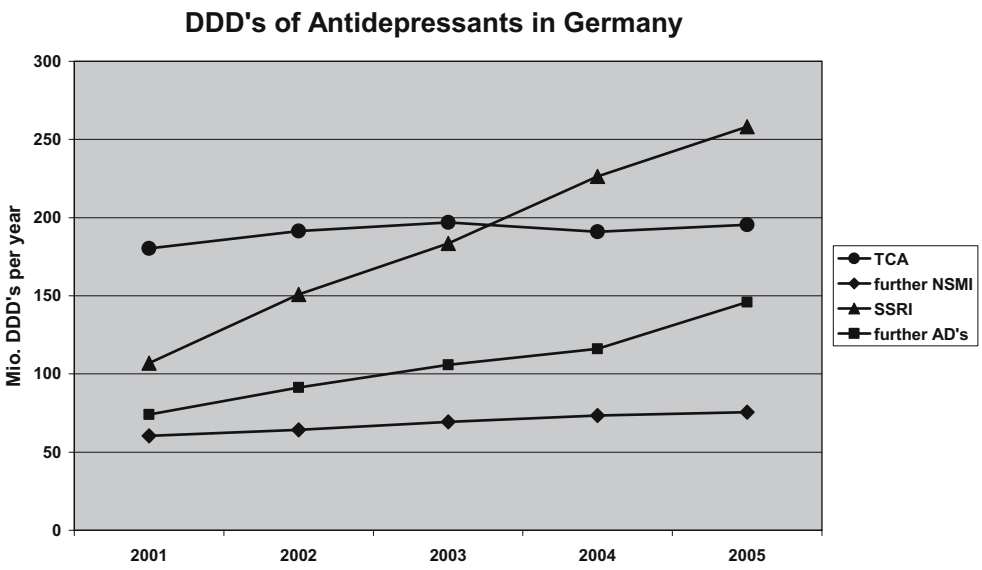

Fig. 1 Frequency of DDDs of anti-depressants prescribed in Germany at the expense of the GKV (compulsory health insurance) [5–9]

may emerge as a side effect of SSRI uptake and causes the suicidality [27]. Drug-related death with narcotics is also often associated to ADs. In most cases of a drug death, a strict distinction between an intentional (suicidal) or a non-intentional (accidental) overdose cannot be drawn. Drug-related death cases were analysed in a separate group.

Materials and methods

The Institute of Forensic Medicine of the Ludwig-Maximilians-University (LMU) of Munich covers an area of approximately 5 million inhabitants of Southern Bavaria (Germany). Between 2001 and 2005, 11,508 forensic autopsies were performed; of

Table 1 DDDs prescribed in Germany during 2001 and 2005 at the expense of the GKV (compulsory health insurance) [5–9] and case numbers of ADs in suicides and drug death cases found in this study

Anti-depressant	DDD	All suicides	Narcotic drug death
	Millions prescribed in Germany	Case numbers	Case numbers
Amitriptyline+amitripyline-*N*-oxide	498.3	25.17	6.00
Doxepin	276.4	58.33	37.08
Trimipramine	133.7	29.17	13.75
Clomipramine	46.6	0.50	0.50
TCA	955	113.17	57.33
Maprotiline	38.8	1.50	0.00
Imipramine	17.9	0.00	0.00
Opipramol	261	13.83	0.25
Nortriptyline	11.6	3.33	1.00
Dibenzepin	5.9	0.00	0.00
Trazodone	7.9	0.50	0.00
Further NSMRI	343.1	19.17	1.25
Citalopram+escitalopram	445.9	25.17	5.50
Fluoxetine	125.5	5.83	2.58
Paroxetine	139	1.00	0.50
Sertraline	211.9	2.33	0.00
Flufoxamine	2.3	0.00	0.00
SSRI	924.6	34.33	8.58
Mirtazapine	219.3	6.33	1.50
Mianserin	13.1	0.00	0.00
Venlafaxine	148	7.00	3.33
Further ADs	380.4	13.33	4.83
Total	2,603.1	180.00	72.00

The reason for non-integer case numbers are cases with more than one AD. To avoid an over-estimation in these cases, the drugs were evenly distributed. For a detailed explanation, see the "Materials and methods" section

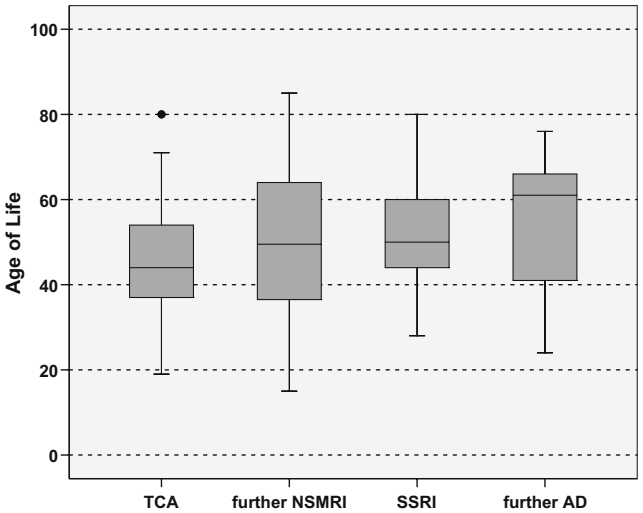

Fig. 2 Age distribution of suicide victims (*boxes* represent the interquartile region (25–75% percentiles), *whiskers* represent the total span)

which, 1,127 were diagnosed as suicides and 704 as narcotic drug death cases (cases in which heroin and/or methadone were the main causes of death). In each of these cases of suicide or narcotic drug death, a blood and, if available, a urine sample were analysed in the forensic-toxicological laboratory of the Institute of Forensic Medicine of the LMU, Munich at least by immunoassay for TCAs (Cedia®) and high-performance liquid chromatography (HPLC) with a scanning ultraviolet-detector to differentiate and quantify most of the ADs approved in Germany.

The applied HPLC method in principle The working-up procedure is as follows: Camazepam (0.5 μg/ml) is added to the cadaver blood for internal standardisation. 1 ml blood is vortexed with 5 ml chlorobutane for 1 min and hard centrifuged. 30 μl ethylenglycole is added to the separated organic layer and the mixture was evaporated at 50°C. The residue is resolved in 70 μl of a mixture of CH_3CN/H_2O (1:1). The HPLC conditions are as follows: column C18, 5 μm; mobile phase: phosphate buffer pH 2.5/acetonitrile 60:40, isocratic; injection volume, 30 μl; wavelength, 230 nm; run time, 45 min.

An ingestion of amitriptyline-*N*-oxide could not be definitely differentiated from an ingestion of amitriptyline. Therefore, both drugs were compiled in one group. Similarly, the *S*-enantiomer escitalopram could not be differentiated analytically from citalopram. Lithium, tranylcypromin, moclobemid and nefazodon could not be detected with the performed routine analysis. Duloxetin was newly introduced in Germany in 2005 and was not included in this evaluation. The ADs, which could be detected with the applied method, are listed in Table 1.

The results were compared to the DDDs of ADs prescribed in Germany during 2001 and 2005 at the expense of the Gesetzliche Krankenversicherung (GKV, compulsory health insurance), which covers approximately 90% of all prescriptions of ADs in Germany. The source of these data were the annual Arzneimittelverordungsreports (drug prescription reports) [5–9]. These reports cover the 3,000 most prescribed medicinal products in Germany. In literature and handbooks, ADs are grouped in different manners. For a better comparison, in the present study, the ADs found in the autopsy cases were grouped according to the WHO Collaboration Centre for Drug Statistics Methodology [4] and the Arzneimittelverordungsreports [5–9] in classic TCAs, further NSMRIs, SSRIs and further ADs, including α_2-antagonists and serotonin–noradrenalin reuptake inhibitors (SNRIs).

Table 2 Relative frequency of the ADs

Antidepressant	Prescribed (DDD)	All suicides		Narcotic drug death	
	%	%	*r*	%	*r*
Amitriptyline +amitiptyline-*N*-oxide	19.14	13.98	0.73	8.33	0.44
Doxepin	10.62	32.41	3.05	51.50	4.85
Trimipramine	5.14	16.20	3.15	19.10	3.72
Clomipramine	1.79	0.28	0.16	0.69	0.39
TCA	36.69	62.87*	1.71	79.63*	2.17
Maprotiline	1.49	0.83	0.56	0.00	0.00
Imipramine	0.69	0.00	0.00	0.00	0.00
Opipramol	10.03	7.69	0.77	0.35	0.03
Nortriptyline	0.45	1.85	4.16	1.39	3.12
Dibenzepin	0.23	0.00	0.00	0.00	0.00
Trazodone	0.30	0.28	0.92	0.00	0.00
Further NSMRI	13.18	10.65 n.s.	0.81.	1.74*	0.13
Citalopram +escitalopram	17.13	13.98	0.82	7.64	0.45
Fluoxetine	4.82	3.24	0.67	3.59	0.74
Paroxetine	5.34	0.56	0.10	0.69	0.13
Sertraline	8.14	1.30	0.16	0.00	0.00
Flufoxamine	0.09	0.00	0.00	0.00	0.00
SSRI	35.52	19.07*	0.54	11.92*	0.34
Mirtazapine	8.42	3.52	0.42	2.08	0.25
Mianserin	0.50	0.00	0.00	0.00	0.00
Venlafaxine	5.69	3.89	0.68	4.63	0.81
Further ADs	14.61	7.41*	0.51	6.71 n.s.	0.46
Grand total	100.00	100.00	1.00	100.00	1.00

Significant results ($p<0.05$) are denoted by an asterisk (*), non-significant results ($p>0.05$) are denoted by "n.s." (non-significant).
r: ratio between the observed number of cases and the number of cases, as expected from the prescription frequency

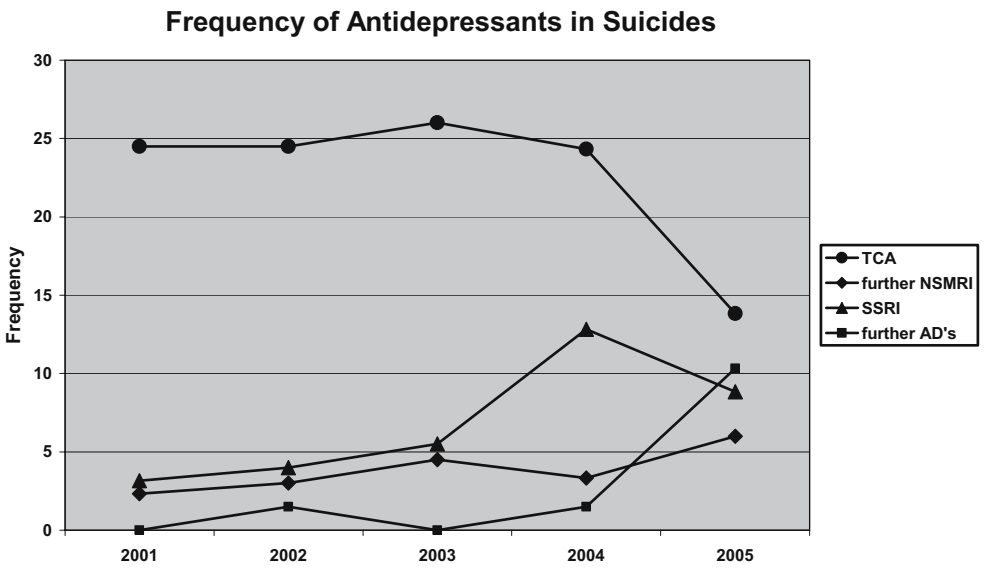

Fig. 3 Frequency of anti-depressants associated to suicides per year

The Public Prosecutor's Department had not ordered an autopsy in each case of a suicide or a drug death. But regarding ADs, the autopsied cases were representative for all suicides and narcotic drug death cases in the area because the ingestion of ADs was not a criteria for the Public Prosecutor's Department to order an autopsy or not. Because an autopsy was not performed in every case of a suicide or drug death, the incidence of death cases to the number of prescribed DDDs [28] was not calculated. Instead, the relative frequency (percentage) of each AD in each group of manner of death (all suicides, ADs responsible for death, other non-violent suicides, violent suicides, drug death) was calculated. In some cases, more than one AD was detected. To avoid an over-estimation, these cases were evenly distributed, e.g. if two ADs were detected in one case, 0.5 for one AD and 0.5 for the other. This explains some non-integer case numbers. The concentrations of different ADs in a case were not taken for further loading. A ratio "r" was calculated as the difference between the observed number of cases and the number of cases, which would be expected from an equal distribution of all ADs according to the prescription frequency.

The suicides were further split into violent ("hard") and non-violent ("soft") suicides. Violent suicides cover deaths caused by self-performed artery cut, self-hanging, jump from a height, run over by a rail vehicle, shot, suffocation or throat cut. Non-violent suicides cover deaths caused by drowning or intoxication with drugs and/or alcohol. The non-violent suicides were further sub-divided into cases in which the ADs were responsible for the death and others. This differentiation was performed according to the final expert opinion of the Institute of Forensic Medicine of

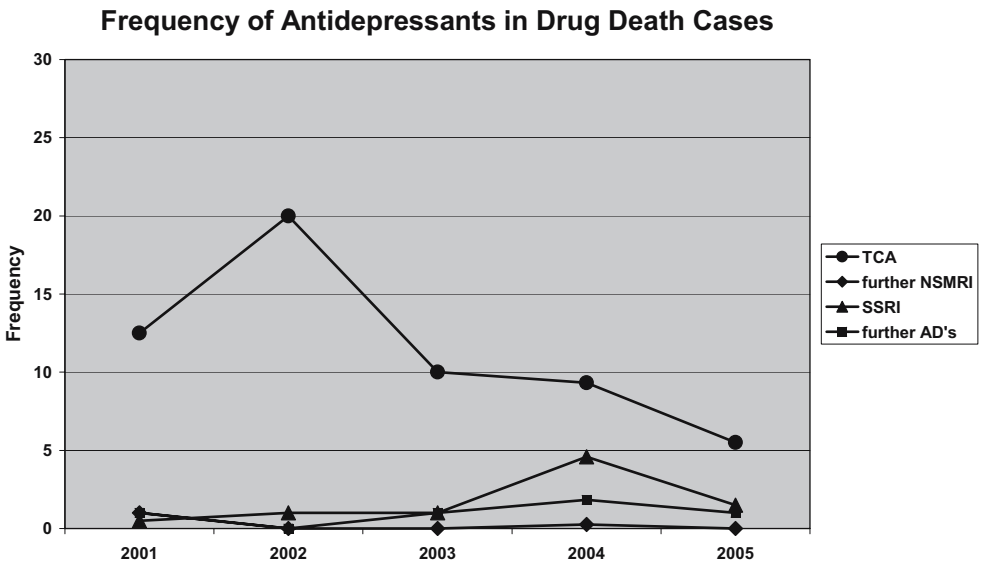

Fig. 4 Frequency of anti-depressants associated to narcotic drug death cases per year

Table 3 Relative frequency of ADs in the sub-groups of suicides

Sub-group of suicide	DDDs	AD responsible for a suicide		Associated to another non-violent suicide		Associated to a violent suicide	
Total number	2,603.1 million	99		51		30	
From these	%	%	r	%	r	%	r
TCA	36.69	73.40*	2.00	63.73*	1.74	26.67 n.s.	0.73
Further NSMRI	13.18	10.27 n.s.	0.78	7.84 n.s.	0.60	16.67 n.s.	1.26
SSRI	35.52	11.95*	0.34	24.51 n.s.	0.69	33.33 n.s.	0.94
Further ADs	14.61	4.38*	0.30	3.92*	0.27	23.33 n.s.	1.60
Total	100.00	100.00	1.00	100.00	1.00	100.00	1.00

Significant results ($p<0.05$) are denoted by an asterisk (*), non-significant results ($p>0.05$) are denoted by "n.s." (non-significant).
For the explanation of "r" see text and Table 2.

Munich to the Public Prosecutor's Department. Cases were very restrictively grouped as "ADs responsible for death". In these cases, either (1) no other drugs except ADs (proven by immunoassay, HPLC and gas chromotography–mass spectrometry screening) and/or alcohol were detected, (2) the additional drugs found were not suitable for an additional adverse effect or (3) the concentration of the additional drugs found was below the therapeutic range and, therefore, an additional adverse effect could be excluded. All other cases of drug and/or alcohol combinations were grouped as "other non-violent suicides".

In the drug-related death cases with narcotics, the ADs did not play a central role in the mortal process. In all these cases, an overdose of heroin and/or methadone was predominantly responsible for the death. In most of these cases, further drugs like benzodiazepines or cannabis were detected. This means that most of these deceased have been multi-drug-dependent.

Statistics was calculated using the SPSS 14.0. For the comparison of observed and expected case numbers, the chi-squared test was used. In the case of case numbers below 5, the exact test (SPSS 14.0) was used. Significant results ($p<0.05$) are denoted by an asterisk (*), non-significant results ($p>0.05$) are denoted by "n.s." (non-significant).

Results

In 180 suicides (16.0% of all autopsied suicides) and 72 narcotic drug death cases (10.2% of all autopsied drug death cases), ADs were found. Figure 2 shows the age distribution of all suicides associated to the different sub-groups of ADs.

Table 1 shows the absolute numbers of the ADs in comparison to the total prescription frequency in Germany expressed in DDDs. In Table 2, the relative frequency in percent of all suicides or drug death cases is listed. The annual changes of the frequency of the AD sub-groups (TCAs, further NSMRIs, SSRIs and further ADs) are plotted in Fig. 3, in the case of suicides and in Fig. 4, in the case of drug overdose.

Table 4 Relative frequency of the five most prescribed ADs in the sub-groups of suicides

Sub-group of suicide	DDDs	AD responsible for a suicide		Associated to another non-violent suicide		Associated to a violent suicide	
			r		*r*		*r*
Total number	1,615.3 million	83.67		45.00		23.00	
% of all ADs	62.05	84.51*	1.36	88.24*	1.42	76.67 n.s.	1.24
Amongst these							
Amitriptyline+amitiptyline-*N*-oxide	19.14	16.33 n.s.	0.85	9.80 n.s.	0.51	13.33 n.s.	0.70
Doxepin	10.62	35.19*	3.31	40.20*	3.78	10.00 n.s.	0.94
Trimipramine	5.14	21.38*	4.16	13.73*	2.67	3.33 n.s.	0.65
Opipramol	10.03	4.88 n.s.	0.49	7.84 n.s.	0.78	16.67 n.s.	1.66
Citalopram+escitalopram	17.13	6.73 n.s.	0.39	16.67 n.s.	0.97	33.33 n.s.	1.95

Significant results ($p<0.05$) are denoted by an asterisk (*), non-significant results ($p>0.05$) are denoted by "n.s." (non-significant).
For the explanation of "r" see text and Table 2.

Despite the high total number of cases in this study, the frequency of some rarely prescribed ADs was too low for a sound further differentiation. Therefore, a further subdivision to "AD(s) responsible", "other non-violent" and "violent" suicides was performed only for the AD subgroups (TCAs, further NSMRIs, SSRIs and further ADs) (Table 3) and for the five most found ADs (amitriptyline, doxepin, trimipramine, opipramol and citalopram) (Table 4).

Discussion

The boxplots in Fig. 2 give no indication for a special suicidal problem of SSRIs in juveniles. Within 5 years, no case of SSRIs was found in a suicide victim younger than 28 years in an area of approximately 5 million people and 1,127 autopsied suicides. As discussed in the "Materials and methods" section, not every suicide in the area was autopsied, e.g. if the suicide was beyond doubt, well-documented by the circumstances, a suicide note, etc. According to the common procedure of the Public Prosecutor's Department, in every un-expected sudden death of a child or a juvenile, an autopsy was performed. Therefore, it seems to be allowed to generalise the result that an association between SSRIs and completed suicides in children or juveniles cannot be proven. Comparable results were reported recently from Leon et al. for New York City [29] and Sondergard et al. for Denmark [30]. From our data, it cannot be differentiated whether this is caused by (1) a restrictive prescription of SSRIs to children and juveniles (due to a warning, as mandatory in the "Fachinformationen" (official information for medical experts) for SSRIs in Germany), (2) no relevant increase of suicidality by SSRIs, as supposed by quite different approaches than ours [13–23, 26, 27, 31] or (3) the fact that there are large differences between suicidal ideas, the intention of a suicidal act (just for demonstration?), a real suicide attempt and the final success of a suicide.

Compared to the prescription frequency, the TCAs doxepin (r=3.05*) and trimipramine (r=3.15*) were over-represented in suicides, whilst the SSRIs paroxetine (r=0.10*), sertraline (r=0.16*) and mirtazapine (r=0.42*) were under-represented (Table 2). In narcotic drug death cases, the over-representation of doxepin (r=4.85*) is striking. This corresponds to our results of the analysis of blood samples from living drug addicts (unpublished data). On the other hand, opipramol with a prescription frequency of 10.03% (*) was found in almost none of the narcotic drug death cases (Table 2).

Amongst suicides in which the ADs have been responsible for the occurrence of death, TCAs were obviously over-represented compared to the expected number of cases by a ratio of 2.00 (*) (Table 3). On the other hand, SSRIs (r=0.34*) and "further ADs" (the α_2-antagonist mirtazapine and the SNRI venlafaxine) (r=0.30*) were under-represented. In other non-violent suicides, also higher numbers of TCAs were found than expected from the prescription frequency (r=1.74*). In contrast, in cases of violent suicides, the distribution of the ADs to the four subgroups (TCA, further NSMRIs, SSRIs and further ADs) reflects more the frequency of prescription with a slight under-representation of the TCAs (r=0.73, n.s.) and an over-representation of the "further ADs" (r=1.60, n.s.) (Table 3). This over-representation was found for the α_2-antagonist mirtazapine (f=1.58) and for the SNRI venlafaxine (r=1.75). Due to the relatively low absolute number of violent suicides associated with mirtazapine (n=4) and venlafaxine (n=3), the results for these two ADs should not be over-interpreted. They are not statistically significant.

The five most prescribed ADs (amitriptyline+amitriptyline-*N*-oxide, doxepin, trimipramine, opipramol and citalopram+escitalopram) cover approximately 80% of all ADs found in suicides (Table 4). In cases associated with doxepin (*) and trimipramine (*), non-violent suicides were distinctly over-represented. In contrast, in cases with citalopram (*) or opipramol (*), violent forms of suicides are over-represented.

Table 5 Case numbers of ADs responsible for death in suicides without TCAs

Anti-depressant	Case numbers
Maprotiline	1
Imipramine	0
Opipramol	3
Nortriptyline	3
Dibenzepin	0
Trazodone	0
Further NSMRI	7
Citalopram+escitalopram	1
Fluoxetine	3
Paroxetine	0
Sertraline	1
Flufoxamine	0
SSRI	5
Mirtazapine	1
Mianserin	0
Venlafaxine	2
Further ADs	3
Citalopram+mirtazapine	2
Citalopram+maprotiline	1
Combinations	3
Total	18

For amitriptyline, the ratio was approximately balanced (Table 5).

The different frequency distribution of the ADs associated to violent and to non-violent suicides may be explained by their different pharmacological active profiles and the different lethality of overdoses of the different ADs. Doxepin and trimipramine act as depressants on the central nervous system (CNS), whilst citalopram and opipramol have a stronger activating component [27]. The lethality of an overdose of TCAs like doxepin and trimipramine is higher than that of opipramol or SSRIs like citalopram [3, 10, 12, 32].

In most cases, TCAs alone or combinations of TCAs with other ADs were responsible for the death (Table 3). But in 18 out of 99 cases of overdoses, other ADs than TCAs were responsible for the death (Table 5).

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