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Research report

Psychopharmacological treatment before suicide attempt among patients admitted to a Psychiatric Intensive Care Unit

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Abstract

Background: It is difficult to assess the effectiveness of treatments in lowering suicide incidence.
Methods: To ascertain the impact of antidepressants (AD) on suicidal behavior, we compared the psychopharmacological treatment taken in the previous 3 months by cases who had made or not a suicide attempt (SA) just before their admission to a hospital.
Results: In comparison with not SA cases, SA cases were more likely to have received AD and benzodiazepines (BZD) before hospitalization. On the contrary, they were less likely to have received antipsychotics, antiepileptic mood stabilizers, and lithium. Similar results were observed when the analysis was restricted to cases with a diagnosis of Major Depression, Bipolar Depression or Bipolar Mixed state, Schizoaffective Disorder, Depressive or Mixed type. Previous AD treatment seemed to be not related to the severity of psychopathology in general or to the severity of depressive and anxiety symptoms.
Conclusions: The results suggest that the use of AD in patients with mood disorders is not associated with a reduction of SA rate. Rather, it is not possible to exclude that AD or BZD can induce, worsen, or precipitate suicidal behavior in some patients, especially in those affected by mood disorders with Depressive or Mixed features. The results must be considered preliminary since this is an open, non-randomized, non-controlled study that was carried out at a single facility.

Keywords: Antidepressants; Bipolar Disorder; Major Depression; Suicide; Treatment

1. Introduction

Suicide is a leading cause of death in the general population. Since suicide is a complex behavior related not only to clinical but also to social factors and systems of care, it is difficult to assess the effectiveness of treatments in lowering suicide incidence. We must recognize that not enough is known about suicidal behavior to justify dogmatic conclusions.

In the research on suicide, Randomized Controlled Trials (RCT) present strong biases, including the following: 1) patients who are very severe, psychotically depressed, with comorbid substance abuse or anxiety disorder, or with known suicide risk, are generally excluded (Zetin and Hoepner, 2007); 2) the setting is characterized by unusually intensive procedures of assessment and treatment; 3) patients and researchers are highly motivated; 4) a relatively low number of patients enter the studies and the follow up is short;

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therefore, the incidence of suicidal behavior is rare; even pooling of data from several hundred RCT may not have sufficient power to detect clinically important risks or benefits; 5) most RCT are funded by pharmaceutical companies.

A large meta-analysis (Gunnell et al., 2005) of 477 RCT of Selective Serotonin Reuptake Inhibitors (SSRIs) compared with placebo in over 40,000 adults submitted by pharmaceutical companies to the safety review of the Medicines and Healthcare products Regulatory Agency could not rule out increased risk of suicide and self-harm caused by SSRIs. The authors concluded that, because of the low incidence of suicide, it was not possible to rule out either a threefold increase or a decrease in its occurrence among people treated with SSRIs. According to these authors, about two millions of patients should be randomized to detect an important effect on risk.

On the other hand, "real world" studies are characterized by methodological shortcomings. To minimize the intrinsic limitations of naturalistic studies, some precautions are warranted: 1) the data should be collected blind to their future use; 2) selection of cases should be controlled or avoided at all; 3) only highly reliable data should be examined; 4) statistical analysis should be cautious and conservative; 5) testing of hypothesis should be based on different and independent evidences; 6) alternative hypotheses should be implausible; 7) clinicians involved in the research should be expert and honest; 8) sponsorship should be avoided.

In order to ascertain the impact of antidepressant treatment on suicidal behavior, we designed the present observational study whose main aims were: 1) to evaluate the Cases who had made a SA immediately before their admission (SA CASES) to a Psychiatric Intensive Care Unit (PICU); 2) to ascertain which psychopharmacological treatment (if any) they had been assuming in the 3 months before admission; 3) to compare such treatment with the treatment taken in the 3 months before admission by Cases admitted to the PICU not after a SA (NOT SA CASES) in the same period of time.

2. Method

The study involved patients admitted to a PICU of a general hospital providing assistance to an urban catchment area of 210,000 inhabitants. According to the Italian law, most voluntary patients and all involuntary patients who reside in this area and who need immediate psychiatric hospitalization are admitted to this PICU. Some cases, who are affected by milder symptoms and can delay immediate hospitalization, are sometimes admitted to private clinics. This offers the unique opportunity to observe most (if not all) cases of serious SA in an unselected sample of patients. With the possible exception of few cases of SA characterized by minimal medical consequences and for whom immediate hospitalization was not warranted, it is legitimate to assume that all SA made in the considered period by residents in the catchment area and managed by health services entered the present study.

Admissions to the PICU exclude persons under age 18. The patients examined were all those discharged between 1 April 2004 and 31 March 2007. The following data were ascertained for each patient: sex, age, diagnosis (DSM-IV-TR), type of admission (voluntary or involuntary), length of hospitalization, aggressive or violent behavior (Morrison, 1992), psychopharmacological treatment in the 3 months preceding admission and in the course of hospitalization, and Clinical Global Impression (CGI). We defined SA as a potentially self-injurious action with a non-fatal outcome for which there is evidence, either explicit or implicit, that the individual intended to kill himself/herself. The action may or may not result in injuries (Moscicki, 1997). Previous psychopharmacological treatment was assessed by asking patients, their relatives, and their treating psychiatrists, and by examining medical charts. If the

Table 1
Socio-demographic and clinical characteristics of SA and not SA cases

	SA cases	Not SA cases	χ^2	*fd*	*P*
Gender (M/F)	59 (45.7%)/70 (54.3%)	647 (52.5%)/586 (47.5%)	1.862	1	.172
Parents (Y/N/U)	51 (39.5%)/72 (55.8%)/6 (4.7%)	362 (29.4%)/782 (63.4%)/89 (7.2%)	6.169	2	.046*
Commitment (Y/N)	23 (17.8%)/106 (82.2%)	258 (20.9%)/975 (79.1%)	0.507	1	.476
Previous SA (Y/N/U)	48 (37.2%)/49 (38.0%)/32 (24.8%)	213 (17.3%)/451 (36.6%)/569 (46.1%)	10.620	2	.001*
			t	*fd*	*p*
Age (Years) (±SD)	44.9(±15.8)	42.1 (±14.6)	2.055	1353	.040*
Hospitalization days	9.9 (±11.7)	10.4 (±11.7)	0.462	1360	.644

M/F = Males/Females; Y/N/U = Yes/No/Unavailable–Unreliable; SA = Suicide Attempt; * = statistically significant.

Table 2
Diagnoses in SA and not SA cases

Diagnosis	SA cases	Not SA cases	χ^2	*fd*	*P*
Schizophrenia	1 (0.8%)	59 (4.8%)	3.558	1	.059
Schizoaffective Disorder (all)	7 (5.4%)	210 (17.3%)	10.892	1	.000*
Schizoaffective Disorder manic	0 (0%)	119 (9.7%)	12.459	1	.000*
Schizoaffective Disorder Depressive	4 (3.1%)	26 (2.1%)	0.172	1	.678
Schizoaffective Disorder Mixed	3 (2.3%)	65 (5.3%)	1.561	1	.212
Unipolar Depression	20 (15.5%)	26 (2.1%)	60.173	1	.000*
Bipolar Disorder (all)	85 (65.9%)	738 (59.9%)	1.537	1	.215
Mania	2 (1.6%)	361 (29.3%)	44.522	1	.000*
Bipolar Depression	27 (20.9%)	80 (6.5%)	31.682	1	.000*
Bipolar Mixed	55 (42.6%)	292 (23.7%)	21.109	1	.000*
Bipolar NOS	1 (0.8%)	5 (0.4%)	0.009	1	.924
Psychosis NOS	4 (3.1%)	92 (7.5%)	2.757	1	.097
Atypical Depression	7 (5.4%)	15 (1.2%)	10.509	1	.001*
Other	5 (3.9%)	93 (7.5%)	1.834	1	.176

SA = Suicide Attempt; * = statistically significant; NOS = Not Otherwise Specified.

patient was taking a drug at the time of admission, a minimum of 3 days of assumptions was required to consider the patient on treatment with that drug. If the patient had suspended a drug in the previous month, a minimum of 15 days of treatment was required to consider the patient "on treatment" with that drug. In as many

Table 3
Clinical assessments in SA and not SA CASES with a diagnosis of Unipolar Depression, Bipolar Depression or Bipolar Mixed state, Schizoaffective Disorder Depressive or Mixed type

Number of cases	SA CASES	Not SA CASES	*t*-test	*fd*	*P*
	109	489			
Age (Years) (±SD)	45.4 (±15.8) [109]	42.6 (±15.1) [489]	1.736	596	.083
Hospitalization days	10.2 (±12.0) [109]	10.9 (±(10.9) [489]	0.595	596	.552
GAF (current)	15.6 (±4.7)	26.5 (±8.0) [453]	−13.310	554	.000*
GAF (last year best)	56.7 (±10.8)	52.2 (±11.9) [368]	3.047	442	.002*
BPRS	57.6 (±11.3) [71]	61.4 (±13.5) [263]	−2.174	332	.030*
BPRS Anx–Dep.	13.6 (±2.9) [71]	11.9 (±3.5) [264]	3.844	333	.000*
BPRS Thought Dis.	7.4 (±3.6) [71]	10.3 (±4.7) [264]	−4.788	333	.000*
BPRS Host–agit.	5.5 (±2.8) [71]	7.6 (±3.4) [263]	−4.803	332	.000*
BPRS Excitement	6.8 (±2.8) [71]	7.7 (±3.7) [264]	−1.866	333	.063
BPRS Retirement	6.4 (±3.9) [71]	7.2 (±3.9) [264]	−1.462	333	.145
SAPS	14.8 (±13.4) [71]	29.5 (±22.2) [263]	−5.320	332	.000*
SANS	33.1 (±22.7) [71]	43.7 (±23.4) [263]	−3.470	332	.000*
MMSE	27.4 (±2.6) [66]	27.3 (±2.7) [250]	0.215	314	.830
			χ^2	*fd*	*p*
Gender (M/F)	49 (45.0%)/60 (55.0%)	215 (44.0%)/274 (56.0%)	0.007	1	.935
Parents (Y/N/U)	46 (42.2%)/60 (55.0%)/3 (2.8%)	189 (38.6%)/281 (57.5%)/19 (3.9%)	0.689	2	.709
Commitment (Y/N)	19 (17.4%)/90 (82.6%)	56 (11.5%)/433 (88.5%)	2.386	1	.122
Previous SA (Y/N/U)	43 (39.5%)/41 (37.6%)/25 (22.9%)	129 (26.4%)/195 (39.9%)/165 (33.7%)	8.685	2	.013*
CGI score: 4	2 (1.8%)	12 (2.5%)			
CGI score: 5	26 (23.9%)	92 (18.8%)			
CGI score: 6	79 (72.5%)	376 (76.9%)			
CGI score: 7	2 (1.8%)	9 (1.8%)			
			8.096	3	.057

Number of compared cases in square brackets; M/F = Males/Females; Y/N/U = Yes/No/Unavailable–Unreliable; SA = Suicide Attempt; * = statistically significant.
Anx–Dep. = Anxiety–Depression; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning Scale; Host–agit. = Hostility–agitation; MMSE = Mini Mental State Examination; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; Thought Dis. = Thought Disorder.

patients as possible, on admission, we assessed clinical conditions by the Brief Psychiatric Rating Scale (BPRS), including 24 items, the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the Mini Mental State Examination (MMSE), the Global Assessment of Functioning Scale (GAF). For purposes of data analysis, we combined the BPRS items into five summary scores: 1) *Psychotic cluster* which includes *Conceptual disorganization, Grandiosity, Hallucinatory behavior*, and *Unusual thought content*; 2) *Withdrawal–Retardation cluster* which includes *Motor retardation, Emotional withdrawal*, and *Blunted affect*; 3) *Hostility–Suspiciousness cluster* which includes *Hostility, Suspiciousness*, and *Uncooperativeness*; 4) *Anxiety–Depression cluster* which includes *Anxiety, Depression,* and *Guilt*; 5) *Grandiosity–Excitement cluster* which includes *Elevated Mood, Grandiosity, Excitement*, and *Motor Hyperactivity.* The duration of the time frame for assessment was 7 days for the BPRS, SAPS and SANS. Clinical evaluations were made by senior psychiatrists (MR, AA) with over 20-years of professional experience. Final longitudinal best-estimate assessment was generated by authors' consensus. The χ^2 test was used to analyze categorical variables. *t*-test was performed for continuous variables. All *p* values were two tailed, and statistical significance was set at $p<0.05$.

3. Results

3.1. Entire sample

In the considered period, SA CASES were 129 (9.5%), while NOT SA CASES were 1233 (90.5%). The differences between the two groups are shown in Tables 1 and 2.

In the 3 months preceding hospitalization, in comparison with NOT SA CASES, SA CASES were more likely to have received AD [50/129 (38.8%) vs 191/1233 (15.5%); ($\chi^2=41.834$; $fd=1$; $p=.000$)] and Benzodiazepines (BZD) [56/129 (43.4%) vs 289/1233 (23.4%); ($\chi^2=23.584$; $fd=1$; $p=.000$)]. On the contrary, they were less likely to have received antipsychotics [42/129 (32.5%) vs 622/1233 (50.4%); ($\chi^2=14.249$; $fd=1$; $p=.000$)], antiepileptic mood stabilizers [29/129 (22.5%) vs 431/1233 (34.9%); ($\chi^2=7.577$; $fd=1$; $p=.006$)], and lithium [3/129 (2.3%) vs 191/1233 (10.5%); ($\chi^2=7.929$; $fd=1$; $p=.005$)].

Table 4
Clinical assessments in SA CASES with a diagnosis of Unipolar Depression, Bipolar Depression or Bipolar Mixed state, Schizoaffective Disorder Depressive or Mixed type who had been treated with antidepressants in the 3 months preceding hospitalization (SA AD CASES) or not (SA not AD CASES)

Number of cases	SA AD cases	SA Not AD cases	*t*-test	*fd*	*P*
	45	64			
GAF (current)	16.3 (±4.4) [43]	15.0 (±4.9) [60]	1.396	101	.166
GAF (last year best)	57.2 (±10.9) [30]	56.4 (±10.9) [46]	0.308	74	.759
BPRS	58.2 (±12.1) [31]	57.3 (±10.9) [41]	0.328	70	.744
BPRS Anx–Dep.	14.3 (±2.2) [31]	13.1 (±3.3) [41]	1.744	70	.086
BPRS Thought Dis.	6.8 (±3.3) [31]	7.9 (±3.8) [41]	−1.319	70	.192
BPRS Host–agit.	5.8 (±3.3) [31]	5.5 (±2.3) [41]	0.418	70	.678
BPRS Excitement	6.9 (±2.4) [31]	6.8 (±3.1) [41]	0.191	70	.849
BPRS Retirement	6.2 (±3.8) [31]	6.5 (±4.0) [41]	−0.329	70	.743
SAPS	12.3 (±12.0) [31]	17.3 (±14.3) [41]	−1.582	70	.118
SANS	33.2 (±22.7) [31]	32.7 (±22.7) [41]	0.083	70	.934
MMSE	27.6 (±2.6) [28]	27.2 (±2.6) [38]	0.551	64	.584
			χ^2	*fd*	*p*
CGI score: 4	1 (2.2%)	1 (1.6%)			
CGI score: 5	10 (22.2%)	16 (25.0%)			
CGI score: 6	34 (75.6%)	45 (70.3%)			
CGI score: 7	0 (0%)	2 (3.1%)			
			1.655	3	.886

Number of compared cases in square brackets.
SA = Suicide Attempt; Anx–Dep. = Anxiety–Depression; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning Scale; Host–agit. = Hostility–agitation; MMSE = Mini Mental State Examination; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; Thought Dis. = Thought Disorder.
* = statistically significant.

Thirty-eight SA CASES (29.5%) and 377 NOT SA CASES (30.6%) did not take any psychopharmacological treatment in the 3 months preceding hospitalization. The difference is not significant (χ^2=2.642; *fd*=2; *p*=.267).

3.2. Comparison between SA and NOT SA CASES with a mood diagnosis

To compare more homogeneous groups and to focus the analysis on the cases more relevant with respect to the aims of the study, we considered only cases with a diagnosis of Major Depression, Bipolar Depression (Bipolar disorder type I or II) or Bipolar Mixed state, Schizoaffective Disorder, Depressive or Mixed type. Five hundred ninety-eight cases met criteria for these diagnoses. Among them, SA CASES were 109 (18.2%), and NOT SA CASES 489 (81.8%). The differences between the two groups are shown in Table 3. In comparison with NOT SA CASES, SA CASES were more likely to receive a diagnosis of Unipolar Depression, Bipolar Depression, or Depressive Schizoaffective Disorder [51/109 (46.8%) vs 132/489 (27.0%); χ^2= 7.415, DF=1; *p*=.006] and received higher scores of BPRS *Anxiety–Depression cluster* (Table 3), reflecting more severe symptoms of depression or anxiety. NOT SA CASES received worse scores on most of the scales, with the exception of current GAF (where SA CASES received a worse score determined by their SA) and BPRS *Anxiety–Depression cluster* (where SA CASES received higher scores reflecting more severe symptoms of depression or anxiety). In the 3 months preceding hospitalization, in comparison with NOT SA CASES, SA CASES were more likely to have received AD [45/109 (41.3%) vs 122/489 (24.9%); (χ^2=11.019; *fd*=1; *p*=.000)] and BZD [49/109 (44.9%) vs 143/489 (29.2%); (χ^2=9.385; *fd*=1; *p*=.002)]. On the contrary, they were less likely to have received antipsychotics [38/109 (34.9%) vs 269/489 (55.0%); (χ^2=13.688; *fd*=1; *p*=.000)], antiepileptic mood stabilizers [28/109 (25.7%) vs 205/489 (41.9%); (χ^2=9.207; *fd*=1; *p*= .002)], and lithium [3/109 (2.7%) vs 64/489 (13.1%); (χ^2=8.560; *fd*=1; *p*=0.003)].

3.3. Comparison between SA CASES with a diagnosis of Bipolar and Unipolar Depression

Eight cases with Unipolar Depression (40%) and 13 with Bipolar Depression (47%) had been treated with

Table 5
Clinical assessments in not SA CASES with a diagnosis of Unipolar Depression, Bipolar Depression or Bipolar Mixed state, Schizoaffective Disorder Depressive or Mixed type who had been treated with antidepressants in the 3 months preceding hospitalization (not SA AD CASES) or not (not SA not AD CASES)

Number of cases	Not SA AD cases	Not SA Not AD cases	*t*-test	*fd*	*P*
	122	367			
GAF (current)	28.2 (±9.0) [116]	25.9 (±7.5) [337]	2.712	451	.007*
GAF (last year best)	54.8 (±11.1) [93]	51.3 (±12.0) [275]	2.462	360	.014*
BPRS	58.5 (±14.4) [73]	62.5 (±12.9) [190]	−2.163	261	.031*
BPRS Anx–Dep.	12.5 (±3.6) [73]	11.7 (±3.4) [191]	1.710	262	.088
BPRS Thought Dis.	8.4 (±4.1) [73]	11.0 (±4.7) [191]	−4.173	262	.000*
BPRS Host–agit.	6.8 (±3.2) [73]	8.0 (±3.4) [190]	−2.444	261	.015*
BPRS Excitement	7.0 (±3.2) [73]	7.9 (±3.8) [191]	−1.937	262	.054
BPRS Retirement	7.5 (±4.0) [73]	7.1 (±3.9) [191]	0.756	262	.450
SAPS	20.5 (±18.1) [73]	33.0 (±22.6) [190]	−4.198	261	.000*
SANS	44.4 (±24.3) [73]	43.4 (±23.0) [190]	0.308	261	.759
MMSE	27.1 (±3.1) [69]	27.4 (±2.6) [181]	−0.756	248	.451
			χ^2	*fd*	*p*
CGI score: 4	5	7			
CGI score: 5	31	61			
CGI score: 6	86	290			
CGI score: 7	0	9			
			9.40	3	.031*

Number of compared cases in square brackets.
SA = Suicide Attempt; Anx–Dep. = Anxiety–Depression; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning Scale; Host–agit. = Hostility–agitation; MMSE = Mini Mental State Examination; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; Thought Dis. = Thought Disorder.
* = statistically significant.

AD. Two cases with Unipolar Depression (10%) and 7 with Bipolar Depression (25.9%) had been treated with mood stabilizers. The differences are not significant.

3.4. Comparison between cases previously treated or not with AD

Had been SA CASES treated more frequently with AD and BZD for their symptoms or had these drugs precipitated SA? To find out answers to this question, we analyzed the differences between SA CASES who had been treated with AD (AD treated SA CASES) or not (NOT AD treated SA CASES) in the 3 months preceding hospitalization, as well as between NOT SA CASES who had been treated with AD (AD treated NOT SA CASES) or not (NOT AD treated NOT SA CASES) in the 3 months preceding hospitalization.

We found no significant difference between AD treated SA CASES and NOT AD treated SA CASES in the scores of GAF, BPRS, SAPS, SANS and MMSE (Table 4). Therefore, on admission, in SA CASES, previous AD treatment seemed not related to the severity of psychopathology in general or to the severity of depressive and anxiety symptoms. In comparison with AD treated NOT SA CASES, NOT AD treated NOT SA CASES received worse scores in GAF, BPRS total, BPRS *Thought disorder* cluster, BPRS *hostility–agitation* cluster, SAPS reflecting more severe psychotic or positive symptoms. The difference in BPRS *Anxiety–Depression* score was not significant between these two groups (Table 5). Therefore, on admission, in NOT SA CASES, previous AD treatment seemed inversely related to the severity of positive psychotic symptoms and not related to the severity of depressive and anxiety symptoms.

4. Discussion

In this study, there are strong limitations that must be acknowledged.

First, it is an open, non-randomized, non-controlled study. However, some of its characteristics make it hard for several bias to enter even if the study is naturalistic. When we collected the data, we had not planned this study yet. Therefore evaluation bias related to the aims of the study seems unlikely. The two crucial variables considered in the study (SA and previous psychopharmacological treatment) are fully objective and unrelated to authors' interventions. It should be said that eight of the 10 psychiatrists who managed the cases in the PICU in the considered period were not involved in the study. Thus, clinical management and outcome evaluation can be considered not influenced by the study.

Second, while nearly all serious SA, occurred in our catchment area and needing medical management, entered the study, it is likely that a substantial number of minor SA not needing medical care escaped our observation.

Third, the retrospective nature of the information about previous treatment deserves cautious interpretation. The reliability of retrospective recall is an inescapable problem. Reliability decreases as the time between ascertainment and the considered period of time increases. In the present study, the duration of the time frame for assessment was relatively short. Multiple informants reduced but not abolished the possibility of false recall, lies, and omissions.

Fourth, the study was carried out at a single facility. Specific hospital practices may have influenced the results. However, the two crucial variables examined in the study (SA and previous psychopharmacological treatment) were not influenced by the practice of the center. SA occurred outside the hospital. Psychopharmacological treatment in the 3 months preceding hospitalization had been prescribed by 160 psychiatrists not involved in the study.

There are also some strengths that should be noted. First, a large series of patients who were clinically well characterized was examined. Second, there were not exclusion criteria in patients' selection. Third, the sample is unselected, including most of (if not all) the serious SA occurred in the catchment area. Fourth, the main results of the study are statistically robust. Fifth, the study was not supported.

The main results are the following: 1) Most (70%) SA CASES, as well as NOT SA CASES, were being treated in the 3 months preceding hospitalization. 2) SA CASES were more likely to have been treated with AD and BZD and less likely to have been treated with antipsychotics, antiepileptic mood stabilizers, and lithium in the 3 months preceding admission. Consistent results were obtained when the analysis was focused on cases with a diagnosis of Major Depression, Bipolar Depression or Bipolar Mixed state, Schizoaffective Disorder, Depressive or Mixed type.

These results could seem trite. One might hypothesize that patients who attempted suicide are those who received more frequently a diagnosis of Unipolar, Bipolar or Schizoaffective Depression or were affected by the more severe forms of mood disorders and were more likely to have been treated with AD for this reason. However, other results suggest a different interpretation. First, the percentage of patients who had not been treated with any psychopharmacological treatment in the 3 months before hospitalization was not different

between SA CASES and NOT SA CASES. This indicates that, for patients affected by mood disorders, being at impending risk of SA was not related with likelihood of being treated. If severer symptoms of depression or higher suicide risk had prompted clinicians to more frequent use of AD, the percentage of untreated patients should have been lower in SA cases. Second, on admission there was no significant clinical difference between AD treated SA CASES and NOT AD treated SA CASES. NOT AD treated NOT SA CASES were affected by more severe psychotic symptoms but by similar symptoms of depression or anxiety in comparison with AD treated NOT SA CASES. Therefore, previous use of AD was not related with more severe depressive or anxious symptoms.

Taken together the results of this study suggest that the use of antidepressants in patients with mood disorders is not associated with a reduction of SA rate. Furthermore, from the present study it is not possible to exclude that AD or BZD may induce, worsen, or precipitate suicidal behavior in some patients, especially in those affected by mood disorders with Depressive or Mixed features.

While it is well known that many patients with a diagnosis of Major Depression are at suicidal risk, it is not always recognized that a substantial portion of these patients has an agitated depression, mixed symptoms of mania, or a bipolar II depression. The current classification of mental disorders does not recognize the specific features of agitated depression. However, it may be crucial to recognize this syndrome. Several authors emphasize that this disorder should be best regarded as "pseudo-unipolar" according with classical German concepts of agitated depression as a mixed state (Koukopoulos and Koukopoulos, 1999; Akiskal et al., 2005). Therefore, the therapeutic approach should be tailored differently according to the treatment guidelines of Bipolar and not Unipolar Depression (Koukopoulos et al., 2005; Rihmer and Akiskal, 2006). Regarding mixed symptoms, the strict DSM-IV-TR criteria for mixed episodes are fully met only by few patients (Perugi et al., 2001). Actually, most patients affected by mood episodes are affected by symptoms of both polarity, mania and depression (Bauer et al., 2005). According to many experts of mood disorders, the dichotomy Unipolar/Bipolar Depression is becoming more and more questionable (Akiskal and Benazzi, 2006; Angst and Cassano, 2005). Bipolar II disorder is often unrecognized (Hantouche and Akiskal, 2005).

Untreated or inappropriately treated Bipolar Depression is associated with a greater risk of suicide (Suppes et al., 2005; Rihmer, 2007). The debate on the effectiveness or dangerousness of AD in the treatment of mood disorder is still open. There are conflicting views regarding AD treatment and the risk of suicidality based on inconsistent results of available studies (Khan et al., 2003; Healy and Whitaker, 2003; Jick et al., 2004; Gunnell et al., 2005; Fergusson et al., 2005; Tiihonen et al., 2006; Gibbons et al., 2007). Furthermore, the cathartic effect of SA that could improve depression for the next few days is a confounding variable (Jallade et al., 2005). Evidence of specific antisuicidal effects of AD from ecological analyses remains elusive (Baldessarini et al., 2007). The U.S. Food and Drug Administration (FDA) warned of possible worsening of depression or increased suicidality in the course of treatment with the new generation of AD and required a "black box warning" regarding suicidality in children and adolescents to be added to all SSRI labels (Culpepper et al., 2004). On May 2, 2007, the FDA ordered that all AD carry an expanded black box warning incorporating information about an increased risk of suicidal symptoms in young adults 18 to 24 years of age. Interestingly, the new warning was developed after the FDA's Psychopharmacologic Drugs Advisory Committee had not only reviewed the results of comprehensive meta-analyses of an enormous data-set on 99.839 participants who were enrolled in 372 randomized clinical trials of AD conducted by 12 pharmaceutical companies during the past two decades, but also heard from psychiatric experts and from family members who testified about the death of loved ones who had taken AD (Friedman and Leon, 2007).

Regarding BZD, in this sample, their use seems to parallel AD treatment. The more frequent use of BZD in the 3 months preceding hospitalization of SA CASES may reflect a higher prevalence of anxiety, restlessness, agitation, or insomnia in AD treated cases. A specific etiological role of BZD in inducing suicidal behavior is also possible, however. BZD can favor disinhibition and impulsiveness.

Unfortunately, there is no definitive answer to the question whether AD or BZD induce or precipitate suicidal behavior in mood disorders. While more data are needed to shed light on this topic, it is safe to conclude that guidelines for the treatment of Bipolar Depression appear less risky than guidelines for the treatment of Unipolar Depression. Probably, it could be safer consider every depressive episode as bipolar (until otherwise proved) instead of unipolar and start treatment with a mood stabilizer, avoiding the risk of precipitating mixed states, agitation, and suicidal behavior by AD monotherapy. The adjunct of BZD should be carefully considered. Anxiety, restlessness, irritability, dysphoria, agitation, or insomnia should alert the clinician about

the possible presence of an agitated depression or of a mixed state. Reconsidering the use of AD, adding a mood stabilizer or a 2nd generation antipsychotic could be first option rather than adding BZD to treatment.

When prescribing AD, clinicians should warn patients of the possible risk of suicidal feelings, thoughts or behavior and monitor patients closely.

Due to the strong limitations of the study, the results must be considered preliminary and the underlying hypotheses need stronger confirmation.

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Conflict of interest

All the authors declare that there is no conflict of interest.

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