Special review

Do antidepressants t(h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant–suicidality FDA advisory in light of declining national suicide statistics from many countries

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Abstract

Given that suicidality is a well-known symptom and outcome of *untreated or inadequately treated* depressive illness, the United States (US) Food and Drug Administration (FDA) warning of emergent suicidality in children and adolescents based on the antidepressant arm of placebo-controlled randomized trials (RCTs) has created understandable concern in clinical practice. The issues involved are of broader public health importance for all age groups. As in other branches of medicine, psychiatrists must always be vigilant of the rare risk of iatrogenesis when prescribing potent agents like antidepressants for patients with depressive disorders where the risk of suicidality is *inherent*. The overall evidence we review suggests that the widespread use of antidepressants in the new "SSRI-era" appear to have actually led to highly significant *decline* in suicide rates in most countries with traditionally high baseline suicide rates. The decline is particularly striking for women who, compared with men, seek more help for depression. Recent clinical data on large samples in the US too have revealed a protective effect of antidepressant against suicide.

We argue that the discrepancy between RCTs (in children) and national and clinical suicide statistics (in adults) may reside in new provocative data documenting high rates of unrecognized pseudo-unipolar mixed states particularly in juvenile, but also in adult, clinical populations. Such an interpretation accords well with equally provocative data that bipolar II (which is often "mixed" in nature) may well represent a particularly vulnerable clinical substrate for suicidality. In this respect, the widespread (at least in the psychiatric sector) augmentation of antidepressants with benzodiazepines, atypical antipsychotics or mood stabilizers may represent one situation where current practice is superior to evidence-based medicine. We conclude that rather than being a threat, the judicious clinical use of antidepressants actually does serve to effectively treat and indeed protect depressed patients from suicidal outcome. The fact of being in treatment with regular clinical follow-up appears beneficial as well.
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1. The background of the antidepressant–suicidality controversy

Untreated or unsuccessfully treated major mood disorders are the main clinical substrates of suicidal behavior (Angst et al., 1999; Rihmer and Kiss, 2002; Baldessarini et al., 2003). Prospective and retrospective studies clearly support the evident clinical observation, i.e. if major mood disorder patients committ or attept suicide, they do it mostly during a major depressive episode (79–89%) and less frequently in dysphoric mania (11–20%), but practically almost never during euthymia (0–1%) (Rouillon et al., 1991; Isometsa et al., 1994; Tondo et al., 1998). On the other hand, patients with anxiety disorders, a population also frequently exposed to antidepressant (AD) pharmacotherapy, experience suicidal behavior mainly in the case of "comorbid" depressive episode (Warshaw and Keller, 1996).

Therefore, to treat mood and anxiety disorders effectively, and to stabilize the period of well-being is crucial for suicide prevention (Khuri and Akiskal, 1983). However, as it has recently been advised by US Food and Drug Administration (FDA, 2004), antidepressants (ADs) could sometimes be related to suicidal behavior, which in their database examined mainly pertains to children and adolescents. New meta-analyses have confirmed FDA's position for a modestly increased risk of suicidality in juvenile patients in SSRI trials (Hammad et al., 2006). We concur with Baldessarini et al.'s (2006) commentary to the effect that this claim is not based on prospectively "defined research outcomes of the trial designs." We also concur with Cheung et al. (2006) that data on antidepressants in children and adolescents should not be extrapolated from adults. Nor should one be tempted to extrapolate to adults from the FDA Advisory on juvenile patients. Nonetheless, the problem is of broader public health significance for all age groups. If suicidality potential of (some) ADs does actualize, it must be small enough to be masked by currently favorable trends in national suicide rates. Even one case of an AD-related suicide is one more than needed, and psychiatrists should identify the vulnerable patients and develop effective prevention strategies to avoid such iatrogenesis. We decided to write this paper because the issues raised by the FDA

cannot be understood solely on the basis of the methodology of the psychopharmacologic trials (Mann et al., 2006) and require consideration of broader epidemiologic and clinical parameters.

In the present review and clinical reformulation of this public health problem, suicidality refers to suicide proneness as evidenced by ideation, verbalization, written communication, or attempt; suicide denotes the completed act that results in death. It would be useful to clarify at this early stage in this paper that what the FDA advisory is warning about, is mainly whether antidepressants are involved in suicidaltiy in the broadest sense, rather than completed suicide. After examining all sides of this controversy, we will argue that the proper use of the FDA advisory can nonetheless serve to develop a rational prevention strategy of how to deal with the suicidality even before it develops.

2. Antidepressants and suicide at the level of general population

Since successful acute and long-term treatment of unipolar depression and bipolar disorders substantially reduces the suicide morbidity and mortality even in this high-risk population (Angst et al., 2002; Baldessarini et al., 2003; Rihmer and Kiss, 2002; Yerevanian et al., 2003, 2004), it is logical to postulate that if the rate of treated depression in the population increases gradually, at a given point will result in a decrease of the suicide rate. Indeed, a prospective trial on Gotland, a Swedish island, showed that educating primary care physicians on how to diagnose and treat depression does lead to a significant decline of suicide rates over a 3-year period, and that this decrease was a linear consequence of the significant decrease of depression-related suicides (Rutz et al., 1989; Rihmer et al., 1995).

However, since the effect of a given intervention depends on the baseline condition (i.e. the effect is greater when the baseline condition is more pathological), the role of more widespread treatment of depression in reducing suicide rates can be easier to detect in countries where the suicide rate is high and the rate of treated depressions is low. Indeed, looking at the countries with the highest suicide rate of the World 20 years ago (between 20 and 46 per 100,000 per year), the

Table 1
Changes in national suicide rates between 1980/1981 and 2001/2003

Country	1980/ 1981	2001/ 2003	Change in percent		
			Total	Males	Females
1. Hungary	44.9	27.7	−38	−30	−55
2. Estonia	36.7	27.3	−26	−19	−45
3. Russian Federation	34.6	38.7	+12	+83	−23
4. Lithuania	33.6	42.1	+25	+25	+30
5. Latvia	32.8	26.0	−21	−27	−35
6. Slovenia (from 1985)	32.8	25.1	−24	−24	−27
7. Denmark	31.6	13.6	−57	−51	−68
8. Austria	25.7	17.9	−30	−12	−38
9. Finland	25.7	20.6	−20	−23	−6
10. Switzerland	25.7	18.4	−28	−28	−30
11. Ukraine	23.7	26.1	+10	+14	−10
12. Belgium (1980–1997)	22.1	21.1	−6	+9	−29
13. Czech Rep. (from 1986)	20.9	16.9	−19	−10	−43
14. France	19.4	17.6	−9	−5	−8
15. Sweden	19.4	13.4	−31	−32	−28
16. Germany (from 1990)	17.8	13.5	−24	−18	−35
17. Slovakia (from 1992)	15.0	13.3	−11	−7	−21
18. Canada	14.0	11.9	−15	−14	−24
19. Norway	12.4	10.4	−12	−12	−12
20. USA	11.8	10.7	−9	−5	−24
21. Poland	11.2	15.5	+38	+41	+25
22. Australia	11.0	12.7	+15	+22	−5
23. Iceland	10.5	12.6	+20	+60	−36
24. Netherlands	10.1	9.2	−9	−1	−20
25. UK	8.8	6.9	−22	−8	−54
26. Portugal	7.4	11.7	+58	+69	+26
27. Italy	7.3	7.1	−7	+9	−18
28. Ireland	6.3	12.7	+102	+158	−5
29. Spain	4.4	8.2	+86	+88	+77
30. Greece	3.3	2.9	−12	0	−37

Countries are listed in decreasing order of their suicide rates at baseline (1980/1981). Suicide rates are expressed as number of siucudes per 100.000/ year. (To avoid the extremely busy nature of this table, only the total suicide rates were entered, i.e. the separate suicide rates of males and females are not shown here).
Source: www.who.org.
Out of these 30 countries, 21 showed decrease and 9 showed increase in suicide rates.
Out of the 13 countries with high baseline suicide rates (20 or more), 10 countries showed decrease (in average 26.9%, range: 6–57%) and 3 showed increase (Russian Fed., Lithuania, Ukraine, all of them are post-Soviet countries). Out of the 17 countries with low baseline suicide rate (less than 20), 11 countries showed decrease (in average 15.0%, range: 9–31%) and 6 showed increase (Poland, Australia, Iceland, Portugal, Ireland and Spain).
Out of the first 10 countries with the highest baseline suicide rates (From Hungary to Switzerland) 2 showed increase (Russian Fed. and Lithuania) and 8 showed decrease (in average 26%, range: 20–57%). Out of the 10 countries with medium baseline suicide rates (from Ukraine to USA) 1 showed increase (Ukraine) and 9 showed decrease (in average 13.1%, range: 6–31%). Out of the 10 countries with the lowest baseline suicide rates (from Poland to Greece), 6 showed increase and 4 showed decrease (in average 12.5%, range: 9–22%). Therefore countries with high baseline suicide rates showed more frequently and more marked decline, and the majority of countries with increasing suicide rates come primarily from countries with low baseline rates.
In the 21 countries with decreased suicide rate, the decrease was greater in females in 19 countries (19/21=90%), while in the 9 countries with increasing suicide rates the increase was higher in males in 8 countries (8/9=89%, chi-square with Yates correction: 14.46, $p=0.0001$). This is in good agreement with the findings of Gotland Study, showing that the decreased number of depressive suicides was almost exclusively the consequence of the decrease in female depressed suicides (Rihmer et al., 1995; Rutz et al., 1997). It has been also repeatedly demonstrated that among suicide victims, females contact much more frequently their GPs or psychiatrists some weeks or months before their death (Rutz et al., 1997; Luoma et al., 2002). It has been also demonstrated that the increase in the utilization of SSRIs is more and less pronounced in females in several countries including Sweden, the United States and Australia (Isacsson, 2000; Hall et al., 2003; Grunebaum et al., 2004).
The detailed analysis of the recent increase of SSRIs and other newer antidepressants in different countries is beyond the scope of this review. However, there is no doubt that the greatest increase can be detected in North America and in Western and nordic Europe (as well as in Hungary) where it has been accompanied by the greatest decrease in the national suicide rates.

24–57% decline in national suicide rates of Denmark, Hungary, Germany, Austria, Estonia, Switzerland, Sweden and Slovenia in the last 2 decades is quite impressive, and a marked (6–8 fold) increase of AD prescription during the same period has been also reported from Denmark, Hungary, Sweden and Finland (Isacsson, 2000; Rihmer, 2001, 2004, see also Table 1). Unemployment and alcohol consumption did not correlate with suicide rates in Sweden (Isacsson, 2000) and in Hungary (Rihmer, 2001), in the two countries where these data were also reported.

On the other hand, in those countries where the suicide rates has always been relatively low (around and below 10 per 100,000 per year), such as Australia, Northern Ireland, Iceland and Italy, the increased utilization of ADs (5-fold increase or less) has not been accompanied by any or marked decline in overall national suicide rates (Barbui et al., 1999; Hall et al., 2003; Kelly et al., 2003; Helgason et al., 2004). Nonetheless, the study from Australia (Hall et al., 2003) also showed that changes in suicide rates were significantly associated with exposure to ADs in different age cohorts between 1990 and 2000: the higher the exposure to ADs, the larger the decline of the suicide rate in a given subpopulation. Moreover, the study from Northern Ireland (Kelly et al., 2003) also demonstrated a significant association between increased AD prescribing and fall in suicide rate in the population over 30 years of age. Unemployment (but not alcohol consumption) was also positively correlated with the suicide rate in this age group.

From 1985 to 1999 the national suicide rate of the United States fell from 12.4 per 100,000 to 10.7 per 100,000 (a 13.5% decline), while the prescription of ADs (mainly SSRIs and other second-generation ADs) increased over 4-fold (Grunebaum et al., 2004). The decline in suicide rate was more pronounced for females (22.5%) than for males (12.8%), consistent with the finding that females received twice as many AD prescription compared with males. Prescription rates for SSRIs and other second-generation ADs in United States between 1985 and 1999 were both inversely and significantly correlated with suicide rates. However, the independent effect of changing rates in unemployment and alcohol consumption has not been demonstrated in this study (Grunebaum et al., 2004). Investigating the relationship between AD utilization and suicide mortality in adolescents, another study from the United States also revealed a significant negative correlation between regional change in AD (mainly SSRIS) utilization and suicide mortality between 1990 and 2000. Doubling in adolescent use of ADs was associated with a decrease of 23 suicides per 100,000 adolescents per year (Olfson et al., 2003). It is important to keep in mind that the foregoing considerations pertain to *completed* suicide, because at least one epidemiologic survey in U.S. adults failed to detect changes in other suicide-related behaviors and/or ideation in the decade of the 1990s (Kessler et al., 2005). Whatever the reasons for this discrepancy–i.e. such behaviors and/or ideation often occur before antidepressants are prescribed–we wish to restate that our main focus in this section is national suicide rates, not the complex and heterogeneous mix of related behaviors and/or ideation.

Investigating the suicide mortality of the 27 countries with data on annual sales of all SSRIs (and other ADs) between 1980 and 2000, Ludwig and Marcotte (2005) have found that after controlling for several socio-demographic factors (unemployment, GDP, gender, age-groups, divorce rate), an increase of one SSRI pill per capita (a 13% increase over 1999 levels) was associated with a 2.5% reduction in suicide rates, a significant relationship that was more pronounced in adults than children. The detailed analysis of these 27 countries also showed that the faster was the growth in SSRI sales per capita, the larger was the decline in suicide rates (Ludwig and Marcotte, 2005).

Of course, the significant negative correlation between increasing AD utilization and decreasing national suicide rates does not automatically suggest a causal association, but considering the strong (and causal) relationship between untreated major mood disorder and suicidal behavior (Angst et al., 2002; Rihmer and Kiss, 2002; Baldessarini et al., 2003; Yerevanian et al., 2003, 2004), all the above mentioned pharmaco-epidemiological studies strongly suggest that more widespread and effective treatment of mood disorders is a significant, but not the only factor in decreasing suicide mortality at the level of the general population. The progressively (and significantly) lowering of suicide rates of depressed patients through the "pretreatment era" (1900–1939), "ECT era" (1940–1959), and "AD era" (1960–1992) (6.3, 5.7, and 3.3 per 1000 patient year, respectively: O'Leary et al., 2001), also support such a connection.

Table 1 provides greater detail on the foregoing national statistics. Countries with the highest baseline suicide rates (except some post-Soviet countries) show the most pronounced declines in their suicide rates. It is also important to highlight that the decline in suicide rates has been striking particularly in females. The same was found in the Gotland trial (Rutz et al., 1989, 1997; Rihmer et al., 1995). These observations accord with the well-known fact that women, compared with men, seek help in greater proportions (Rutz et al., 1997; Luoma et al., 2002). Obviously being in treatment and regular

follow-up by mental help clinicians and general practitioners trained to recognize and treat depression is a necessary ingredient of the therapeutic regimen of clinically depressed patients, especially so when they are suicidal.

3. Antidepressants and suicide in clinical samples of mood disorder patients

Several large-scale, retrospective and/or prospective, naturalistic observational, long-term clinical studies, including severely ill, hospitalized, frequently suicidal mood disorder patients showed that compared to no treatment, the risk of completed suicide among unipolar and bipolar patients on long-term pharmacotherapy (mood stabilizers, ADs) is 2–19 fold lower (Leon et al., 1999; Kallner et al., 2000; Angst et al., 2002; Baldessarini et al., 2003; Yerevanian et al., 2003, 2004). However, since these studies could not exactly discern the successfully and unsuccessfully treated patients as well as medication adherence immediately before the suicide, the difference between successfully treated and unsuccessfully treated nonadherent patients might be much greater.

In spite of the fact that actively suicidal patients are not included into AD drug-studies, randomized controlled trials (RCTs) could provide some useful, albeit limited, information on this topic. Analyzing the committed suicides on the basis of patients exposure years of phase 2–3 RCTs, it has been found that the annual rates of committed suicide were 0.6–0.9% with ADs and 0.3–0.5% with placebo (Rouillon et al., 1991; Kahn et al., 2000, 2001). Comparing the SSRIs, other ADs, and placebo in FDA summary reports of phase 2–3 RCTs (N=48,277, 77 of which completed suicide), the results showed that the annual incidence of committed suicides of patients on SSRIs, on other ADs and on placebo were 0.58%, 0.76%, and 0.45% respectively (Kahn et al., 2003).

The most recent meta-analysis of 702 RCTs, including more than 87,000 depressive and other psychiatric patients, Fergusson et al. (2005) have found a significant increase of suicide attempts for patients taking SSRIs compared with placebo (OR: 2.28). However, focusing on fatal suicide attempts, they did not detect any significant difference between SSRIs and placebo patients.

Much of the recent focus on ADs and suicidal behavior has involved children. The analysis of 25 outpatient pediatric AD-trials, including more than 4000 patients showed that 3.2% of the children taking AD become "suicidal," compared with 1.7% of those taking placebo, but most importantly, no patients in these drug-trials completed suicide (Culpepper et al., 2004; Whittington et al., 2004).

The (nonsignificantly) higher frequency of suicidal behavior on ADs than on placebo in RCTs on unipolar depressives raises several questions. Does it mean that ADs provoke more suicide events than placebo? Does placebo prevent more suicide events than ADs? Do both ADs and placebo provoke suicidal behavior, but this effect is less frequent among patients taking placebo? What would be the frequency of suicidal behavior in this patient population without ADs or placebo (i.e. during the naturalistic course of the illness)? The "evidence-based" findings of the mentioned RCTs in this respect are in sharp contrast with the "evidence" based on the everyday clinical practice, since no clinical guidelines recommend to treat severely ill, acutely suicidal patients with placebo monotherapy! The bizarre nature of this (otherwise logical) conclusion indicates that the basic question ("Do ADs increase or decrease suicidality among depressives?") in this general form is counterproductive and unscientific.

Indeed, short-term RCTs in adults also showed that newly emerged suicidal ideation was rare (3.6% for TCAs, 1.2% for fluoxetine and 2.6% for placebo), and that in 70–72% of the cases, ADs (primarily SSRIS) markedly decreased the suicidal tendencies (that were present in one-third of the patients at baseline), while the same rate for placebo was "only" 55% (Beasley et al., 1991; Montgomery et al., 1995). More recent larger clinical studies, in both adults (Simon et al., 2006) and children (March et al., 2004), have confirmed the protective effects of antidepressants against suicidality. The ACNP task force, which reviewed large RCT database (Mann et al., 2006), also found no evidence that SSRI's were involved in adult suicidality.

Since severely ill, actively suicidal patients, who have the highest lifetime risk of suicide (Bostwick and Pankratz, 2000) as well as DSM-IV diagnosed bipolar depressives, are excluded from AD drug-studies, RCTs are not representative for suicidal depressives. In addition, recent meta-analyses of RCTs have not considered several important factors, such as the time of suicide event (first 3 weeks vs. week 4. or more), the actual clinical condition (nonresponse, response/remission, relapse, etc.), adherence failure (hidden drug-discontinuation before suicide event), and some pharmacokinetic parameters (e.g. excessive metabolization that results in a suboptimal serum-drug level, that can basically influence the drug response, but not the placebo response).

Viewed in perspective, the almost double frequency of suicidal *behavior* (much of it not fatal) of patients on

ADs than on placebo in RCTs (Rouillon et al., 1991; Kahn et al., 2000, 2001, 2003; Whittington et al., 2004) is surprising. Considering the strong anti-suicidal effect of long-term antidepressant pharmacotherapy in open clinical studies on severe unipolar, frequently suicidal depressives (Leon et al., 1999; Angst et al., 2002; Yerevanian et al., 2004), one would have expected a great difference in the opposite direction. The fact that the suicidal behavior of AD-treated unipolar patients in RCTs is just nonsignificantly higher than those of on placebo does not constitute an appropriate answer, as one would have asked "why not much lower"? Does it mean that ADs prevent suicide more frequently among severely ill, frequently suicidal unipolar major depressives, but provoke such behavior sometimes (or prevent less frequently) in less severe, actually nonsuicidal unipolar patients? To answer this, one should look at the complex relationship between ADs and suicide at the individual level.

4. Antidepressants and suicide in individual case studies

As of 1990, several individual case studies appeared in the literature suggesting a link between use of ADs (particularly SSRIs) and suicidal behavior. The dose–response relationship and the challenge–dechallenge–rechallenge nature of these suicidal events suggested that in these cases, the postulated relationship might be real. Most of the authors related the "SSRI-induced suicidal behavior" to the generation of akathisia or agitation (Healy, 2003). The actual clinical condition of the patients at the time when they become suicidal while taking ADs is usually an activated state which is well-known since Kraepelin ("increasing activity before improvement of mood"), but only recently has been termed "an activation syndrome (AS)," that occurs mainly in the initial phase of treatment (Culpepper et al., 2004).

Nearly two decades ago, in a clinical report, Akiskal and Mallya (1987) described a group of an "overzealously" tricyclic antidepressant and MAOI treated outpatients who had developed a refractory agitated depression characterized by: intra-depressive excitatory symptoms, including panic and suicidality, they subsequently responded to lithium- or neuroleptic-augmentation. Another clinical study (Haykal and Akiskal, 1999) also showed that among double depressives given fluoxetine and those who switched from their dysthymic baseline to hyperthymia, eventually mood instability and suicidality emerged; most of these patients had bipolar family history and responded to lithium augmentation. A similar clinical condition

has been described by Koukopoulos et al. (1992). Interestingly, the vast majority of the 10 symptoms of AS, such as agitation, irritability, hostility, impulsivity (and by definition hypomania/mania) are the typical non-euphoric hypomanic symptoms *during* major depressive episode (i.e. depressive mixed state, Koukopoulos and Koukopoulos, 1999; Benazzi, 2002; Benazzi et al., 2002; Akiskal and Benazzi, 2003; Maj et al., 2003; Sato et al., 2003; Akiskal et al., 2005), while other symptoms like anxiety and panic can reflect the high rate of comorbid anxiety disorders found in unipolar but most commonly in bipolar patients (Kessler, 1999; Rihmer et al., 2001). Agitated depression and depressive mixed state (3 or more hypomanic symptoms *during* major depression) appear to be almost identical conditions (Benazzi et al., 2002; Akiskal and Benazzi, 2003; Akiskal et al., 2005), and the clinical cluster of agitated depression/depressive mixed state is associated with increased risk of suicidal behavior (Maser et al., 2002; Benazzi, 2003; Busch et al., 2003; Maj et al., 2003; Akiskal et al., 2005; Akiskal and Benazzi, 2005; Balázs et al., 2006). It is therefore very likely that the AS and AD-induced depressive mixed state–frequently seen in AD-treated depressives with threshold or subthreshold bipolarity (Akiskal and Mallya, 1987; Koukopoulos et al., 1992; Haykal and Akiskal, 1999; Ghaemi et al., 2002; Bottlender et al., 2004)–are the phenomenologic descriptions of the same clinical state from two different angles.

Since the officially diagnosed (DSM-III/IV Type I and II) bipolar depressives are excluded from RCTs on ADs in unipolar major depression, whereas major depressives with subthreshold hypomania and bipolar spectrum depressives (Akiskal and Mallya, 1987; Akiskal and Pinto, 1999; Ghaemi et al., 2002; Dunner, 2003), as well as agitated major depressives (which are closely related to bipolar disorder, Akiskal et al., 2005) are regularly included, we submit results in a substantial proportion of bipolar spectrum patients in the "unipolar" samples in RCTs. In line with these considerations, we wish to cite the landmark study of Rouillon et al. (1991) on prophylactic efficacy of maprotiline and placebo in unipolar depression, where only bipolar I (but not bipolar II) patients were excluded, the rate of all suicidal events during the 1-year follow-up was very much (6-times) higher on maprotiline than on placebo (1.8% vs. 0.3% respectively), which is the largest drug-placebo difference among all RCTs. This may well represent the largest and most systematic database in support for the rare occurrence of suicidality on an antidepressant.

Worsening the clinical picture under treatment with ADs has been recently observed in pediatric population.

Wilens et al. (2003) found that 7% of pediatric patients treated with SSRIs for depression or OCD become manic and 10% become psychotic. Others have reported that the rates of aggressivity, self-injured behavior and homicidal ideation in pediatric patients who developed treatment-emergent mania were 77%, 20% and 6% respectively (Faedda et al., 2004), indicating that the 3–4% of the "depressed" children who become suicidal while on antidepressant (Culpepper et al., 2004; Whittington et al., 2004), should come primarily from early-onset bipolar population (Akiskal, 1995), where the frequency of mixed states is over 70%, a rate being much higher than reported in adult bipolar patients (Dilsaver and Akiskal, 2005).

5. Hypothesis: rare suicidality on antidepressants as iatrogenesis?

In light of the foregoing literature, we submit that the suicidality-antidepressant link appears mediated by depressive mixed states (3 or more hypomanic symptoms during major depressive episode). When ADs worsen depressive illness in some patients, its psychopathological substrate might well reside in an agitated, excited, or mentally aroused–anxious depressive mixed state (Akiskal et al., 2005; Akiskal and Benazzi, 2005). AD monotherapy, unprotected by mood stabilizers or (atypical) antipsychotics, particularly in bipolar and bipolar spectrum disorder (including "unipolar" depressive mixed state) can favor not only hypomanic/manic switches and rapid cycling, but also worsen the pre-existing mixed state or generate de novo mixed conditions at the depressive state or temperament level (Akiskal and Mallya, 1987; Haykal and Akiskal, 1999; Bottlender et al., 2001; Ghaemi et al., 2002; Benazzi, 2003; Dunner, 2003). Recent work, showing that 80% of AD-resistant "unipolar" depressives have threshold and subthreshold bipolar disorder (Sharma et al., 2005), and that among AD-treated outpatients the rate of prior suicide attempts is three-times higher in the case of unrecognized versus recognized bipolarity (Shi et al., 2004) also support this hypothesis.

Another important aspect in the AD-suicidality connection might reside in different neurotransmitter-activity of different (classes of) ADs. Antidepressants with marked norepinephrine reuptake inhibiting potential (e.g. maprotiline, venlafaxine and some TCAs), seem to be associated with more frequent suicidal behavior than SSRIs and placebo (Rouillon et al., 1991; Kahn et al., 2003; Whittington et al., 2004). Analysing almost 15000 suicides in Sweden between 1992 and 2000 that were subjected to forensic toxicological screening, Isacsson et

al. (2005) found that when compared with the average of all antidepressants, the odds ratios showed highly significant underrisks for SSRIs, average risks for TCAs, and overrisks for venlafaxine and mirtazapine. Both of the later mentioned antidepressants have strong serotonergic and noradrenergic activity. Since both central serotonin and norepinephrine/dopamine deficiency ("dysregulation") appear strongly involved in the pathogenesis of depression, but only the hyperactivity of norepinephrine/dopamine (but not serotonin) system is characteristic for (hypo)manic states (Goodwin and Jamison, 1990; Kujawa and Nemeroff, 2000), a hypothetical possibility is that monotherapy with norardenergic ADs is the primary substrate for AS/mixed states (and ultimately aggressive/suicidal behavior). On the other hand, much of the FDA advisory is based on data on selective serotonin re-uptake inhibitors. An earlier related hypothesis formulated by Nutt (1999) proposes that SSRI's do provoke the "activation syndrome," whereas such agents as mirtazapine with combined noradrenergic 5-HT$_2$ mechanism of action might protect form such arousal in the form of anxiety and insomnia, thereby according greater comfort to the acutely depressed patient.

Bipolar disorders, and particularly bipolar II and bipolar spectrum disorder are highly underdiagnosed or misdiagnosed as unipolar depression (Akiskal, 1996; Akiskal and Pinto, 1999; Akiskal et al., 2000; Ghaemi et al., 2002; Dunner, 2003). The very low rate of mood stabilizer treatment in bipolar II patients has also been demonstrated among suicide victims (Rihmer et al., 1990) and among suicide attempters (Balázs et al., 2003). The fact, that out of the three different clinical manifestations of official (DSM-IV, APA, 2000) major mood disorders (unipolar major depression, bipolar I and bipolar II illness), bipolar II diagnosis carries the highest risk for both committed and attempted suicide (Rihmer and Kiss, 2002) further underlines the importance of the correct identification of subthreshold bipolarity among depressed patients (Akiskal and Pinto, 1999).

Worsening medical state, in which the given drug-therapy is effective in general, but could at times be problematic, is also a problem in other fields of medicine. Emergence of resistance to antimicrobial agents is a well-known phenomenon complicating the clinical use of such agents. Provocation of a new arrhythmia or increase in the frequency of preexisting arrhythmia occurs with all antiarrhythmic agents in 6–25% of cases: This so-called "pro-arrhythmogenic" effect can be seen mainly in cardiac patients who have evidence of on-going overt or silent cardiac ischemia (Podrid, 1999). The frequently observed association between lowered serum cholesterol and depression and irritability as well

as suicidal behavior (Kim et al., 2002; Golomb et al., 2004) might be another example that illustrates the potential of rare harm in an otherwise widely used medically beneficial preventive strategy.

6. Concluding remarks

Like other medical fields then, where the risk of iatrogeny is ever present, psychiatry should identify persons who might be threatened by a given intervention. Those depressives who are labile and agitated or otherwise in a mixed state, or give such early warning signs upon antidepressant treatment, must be protected form antidepressant monotherapy (Akiskal et al., 2005; Dilsaver and Akiskal, 2005). Incorporating such observations into everyday clinical practice is urgently needed, as our responsibility in the clinical management of depression is to treat rather than be a threat to the mental health of our patients. This is further discussed in a companion article in this issue of the journal (Benazzi and Akiskal, 2006-this issue). Overall, the data reviewed in this paper justify the claim that the increased use of antidepressants has *reduced* depressive morbidity and suicidal mortality. The formal recognition of depressive mixed states in our official diagnostic system will help to red-flag those pseudo-unipolar mixed depressives for whom antidepressant monotherapy is contra-indicated, and benzodiazepine, mood stabilizer and/or atypical antipsychotic augmentation indicated on clinical grounds (reviewed in Akiskal and Benazzi, 2003). Indeed, this is often what experienced clinicians do worldwide (Fawcett et al., 1997; Akiskal and Pinto, 1999; Furukawa et al., 2001; Smith et al., 2002; Viner et al., 2003; Barak et al., 2006). Because such augmentation is almost never part of research protocols, probably explain why in placebo-controlled trials of antidepressants modest increase in suicidality has been observed. This is an instance where clinical wisdom surpasses evidence-based medicine! However, it is presently unknown to what extent such combined treatment occurs in the general medical sector, where the largest number of depressive patients are treated. Data on this subject will be instructive.

It will be ethically forbidding to attempt to test prospectively the antidepressant–suicide risk potential for the vulnerable few. Psychiatry, like the rest of medicine, is an art based on scientific methodology. Pending further developments in the psychopharmacology and somatotherapy of depressive illnesses, for now the prevention framework outlined herein from various sources of data can be considered the most judicious approach for the clinician. It is encouraging–and in line with the overall thrust of our argument in this review– that a large dataset deriving from clinical practice has upheld the protective effectiveness of antidepressants against suicide (Simon et al., 2006). Another such study has failed to indicate any suicidality associated with antidepressants (Bauer et al., 2006).

Suicide and suicidal behavior are multi-factorial phenomena. We could not obviously cover all relevant biologic and psychosocial factors in the origin and treatment in this paper sharply focused on antidepressants. Obviously clinical vigilance, regular clinical follow-up and supportive therapeutic relationship with physicians and mental health professionals are essential ingredients of suicide prevention.

This review would be incomplete without making reference to lithium. Lithium is well known for its suicide preventive effectiveness in bipolar disorder (see Baldessarini et al., 2003 for a review). Whether such effectiveness extends to the broader spectrum of all affective disorders is a worthy topic of further investigation. To the best of our knowledge–and given its declining use over the past decade–it is unlikely to have had any impact on national suicide rates discussed in the present review.

We wish to sign off with the remark that we earnestly hope that the recently documented decline in the use of antidepressants–at least in American psychiatry (Rosack, 2005)–represents restraint in their use of an understanding of the negative potential of such use in pseudo-unipolar patients. Otherwise such decline in their use could undermine the recent gains in the treatment of depression and, we daresay, in suicide prevention. Whether lithium, mood stabilizer combinations and/or atypical antipsychotics are preferable in such patients are beyond the scope of this commentary.

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