Positive Antidepressant Pharmacotherapy in Reducing Suicide Morbidity and Mortality in Unipolar Depression

a report by

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Abstract

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Although full clinical recovery and good quality of life for the patient is the ideal target in everyday clinical practice, suicide is the most important (and most visible) treatment outcome in patients with psychiatric disorders. A current major depressive episode, particularly in the presence of prior suicide attempts and in the absence of treatment, is the most important medical condition that exists as a risk factor for both completed and attempted suicide.[1,2] The mortality rate due to suicide in mood disorder patients is between 5 and 15%, and among mood disorder patients who have ever been hospitalised the rate is between 15 and 20%.[3]

Prospective and retrospective clinical studies strongly support the evident clinical observation that if major mood disorder patients commit or attempt suicide, they do so almost exclusively in the context of severe major depressive or mixed affective episodes, and very rarely during euthymia and euphoric mania,[2,4–6] indicating that suicidal behaviour in patients with mood disorder is a state- and severity-dependent phenomenon. Therefore, diagnosing and treating acute mood episodes effectively as early as possible and to stabilising the period of euthymia are essential for suicide prevention. Since up to 66% of suicide victims and suicide attempters contact their GPs or psychiatrists four weeks before the suicidal act,[7,8] primary care doctors and psychiatrists play a priority role in suicide prevention.

In the late 1940s (before the 'antidepressant era'), three controlled clinical studies with follow-up periods of 12 months or more compared suicide mortality in depressed patients treated with electroconvulsive therapy (ECT) versus depressed patients who were not treated with ECT. The suicide rates in the non-ECT groups (6.3–7.2%) were much higher than in the ECT groups, indicating a strong protective effect of ECT against suicide in patients with major mood disorders.[9–11]

Some decades later in a six- to 12-month follow-up study of 519 formerly hospitalised unipolar and bipolar depressives, Avery and Winokur[12] found that after six months suicide attempts were seen significantly less frequently in the ECT group (0.8%) than in the antidepressant group (4.2%). However, the rate of completed suicide after one year in the antidepressant group (1.1%) was not significantly different from the ECT group (0%). The authors also found that a history of prior suicide attempt showed a greater risk of both completed suicide (2.9%) and subsequent suicide attempt (5.9%) during the 12-month follow-up.[12] Given the more widespread use of antidepressants in the last few decades, today they *de facto* constitute the first-line treatment of depressive disorders. In this article, we will summarise the role of antidepressants as suicide prevention in patients with unipolar depression.

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Antidepressant Pharmacotherapy and Suicidal Behaviour in Unipolar Depression – Real-world Studies

Recently, several large-scale, retrospective and prospective, naturalistic observational, long-term clinical studies of severely ill and frequently suicidal depressed patients who were usually inpatients took place. This study showed that the risk of completed and attempted suicide among unipolar and bipolar patients on long-term pharmacotherapy (antidepressants and/or mood stabilisers) is markedly reduced compared with no treatment.

In the frame of the National Institute of Mental Health (NIMH) Collaborative Depression Study, Leon et al.[4] analysed the frequency of suicidal behaviour (suicide attempts and completed suicide) of 643 patients with unipolar major depressive disorder between 1988 and 1994. One hundred and eighty-five patients (29%) were treated with fluoxetine, 226 (35%) received other antidepressant treatment (with imipramine equivalence of at least 100mg/day) and 232 (36%) received no antidepressant treatment. More than three-quarters of the patients were previously treated as inpatients and the mean length of follow-up was 4.4 years. The authors found that fluoxetine treatment was associated with a 56% decrease in the risk of suicidal behaviour, and treatment with other antidepressants was associated with a 40% decrease in suicide risk when gender, age and diagnosis at intake, psychopathology and number of previous suicide attempts were controlled. This risk-reduction occurred despite the fact that patients who received fluoxetine or other antidepressants reported many more prior episodes of depression at intake than those who received no antidepressants.[4]

In a 34–38-year naturalistic follow-up study including 186 formerly hospitalised patients with unipolar major depression, Angst et al.[13] found that patients who received long-term pharmacotherapy (lithium, antidepressants, antipsychotics) tended to live longer and to have significantly (2.5-fold) lower suicide rates (7.1 versus 18.1%) than untreated unipolar depressives.

In a comprehensive review of 34 studies (involving 42 groups with lithium maintenance and 25 groups without lithium treatment) including more than 16,000 unipolar and bipolar major mood disorder patients, Baldessarini et al.[14] reported a 21-fold risk reduction in attempted and completed suicides in unipolar or bipolar patients with long-term lithium treatment. In the total sample, the risk reduction was somewhat higher for suicide attempts than for completed suicides (93 versus 82%).

In a subset of patients where bipolar I, bipolar II and unipolar patients were analysed separately, the authors found that for all suicide events, risk reduction was 67, 82 and 100% for bipolar I, bipolar II and unipolar major depressive patients, respectively. The authors concluded that the robust reduction of suicidal behaviour with lithium maintenance treatment in bipolar and particularly with unipolar patients to overall levels was close to general population rates.[14] This marked antisuicidal potential of lithium seems to be more than the simple reflection of its prophylactic effect. It has been demonstrated that during the long-term lithium prophylaxis of 167 recurrent unipolar and bipolar major affective disorder patients with at least one prior suicide attempt, a significant reduction in the number of suicide attempts was found not only in the excellent responders (93%), but also in moderate responders (83%) and non-responders (49%).[15]

Yerevanian et al.[16] compared the rates of suicidal behaviour during and after the discontinuation of long-term antidepressant pharmacotherapy (selective serotonin re-uptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]) of 521 patients with unipolar major depressive disorder and/or dysthymic disorder. The mean duration of follow-up was 24 months (range: six to 132 months). There were four suicides, 27 suicide attempts and 99 hospitalisations for suicidal tendencies during the study period. Rates of all suicide events increased more than five-fold during periods after the discontinuation of antidepressants. Considering the completed suicides only, this increase in the risk was 16-fold. The risk reduction for all suicide events of patients treated with TCAs and SSRIs were 81 and 77%, respectively, suggesting possible protective effects against suicidal behaviour for both TCAs and SSRIs.

Gibbons et al.[17] analysed the suicide attempt rate before and after the initiation of antidepressant monotherapy of more than 226,000 veterans who received a diagnosis of unipolar depressive disorder in 2003 or 2004 and had no history of depression between 2000 and 2002. The findings showed that suicide attempt rates were lower among patients who were treated with antidepressants than those who were not treated, and treatment with SSRIs and TCAs significantly decreased the risk of subsequent suicide attempts. Treatment with SSRIs have shown a protective effect against suicide attempts in all adult age groups.

Investigating more than 82,000 treatment episodes of antidepressant pharmacotherapy (SSRIs and other antidepressants) of 65,103 patients with unipolar major depressive disorder or dysthymic disorder, Simon et al.[18] observed 31 suicide deaths (0.05%) and 76 severe suicide attempts (0.12%) during the six-month follow-up period after beginning antidepressant treatment. These authors also found that the risk of suicide attempts was about 2.5-fold higher in the month before starting antidepressant treatment and declined progressively after starting to take the medication. Considering the fact that antidepressants could mobilise suicidal tendencies (although this is rather rare),[19–22] the authors conclude that "Our data certainly do not exclude the possibility that antidepressant drugs may precipitate increased suicidal ideation or suicide attempts in a subgroup of vulnerable individuals. However, if it occurs such a phenomenon must be infrequent enough to be hidden by the general decline in risk of suicide attempts after starting antidepressant treatment."

However, since the 'real-word' clinical studies discussed above could not exactly discern the successfully and unsuccessfully treated patients as well as medication adherence immediately or some days/weeks before the suicide event, the difference between successfully treated and unsuccessfully treated non-adherent patients may be much greater. However, currently we cannot prevent all suicides. Suicidal behaviour in depressed patients taking antidepressants is relatively most frequent in the first 10 days of the treatment, several days before the start of action of the antidepressants.[18,23]

Register-based observational cohort studies also show that former inpatients with unipolar major depression who continued treatment with antidepressants had a markedly decreased rate of completed suicide

compared with those who stopped taking antidepressants.[24,25] The progressively (and significant) lowering suicide rates of depressed patients through the 'pre-treatment era' (1900–1939), 'ECT era' (1940–1959) and 'antidepressant era' (1960–1992) – 6.3, 5.7 and 3.3 per 1,000 patients per year, respectively[26] – also support the suicide-preventative role of antidepressants in depressed patients. The marked decline of national suicide rates in countries where antidepressant utilisation recently increased by three- to eight-fold also supports this connection,[21,27] suggesting that this beneficial affect could be detected even at the level of the general population. However, it still seems that antidepressant exposure is not adequate to produce a beyond-doubt reduction in suicidal rates in several countries, possibly because of lack of adherence or inadequate dosage prescription.[18,21,27–29]

As between 56 and 87% of suicide victims suffer from current (mostly untreated) major depressive episodes[1–3] and the one-year and current prevalence of major depressive disorders in the general population is 6–8.% and 3–5%, respectively,[30] the short-term change in suicide mortality is hardly independent from the treatment of depressed patients.

In the US after the US Food and Drug Administration (FDA) advisory (black box) warning about the risk of suicide in paediatric patients taking SSRIs for depression, a significant reduction was detected in aggregate rates of diagnosis and treatment of pediatric depression.[31] In fact, in both the US and The Netherlands, the 22% decrease in SSRI prescriptions for youth depressives after the FDA black box warning was followed by an increased rate in youth suicide between 2003 and 2005 of 14 and 49%, respectively. In contrast, in the US, SSRI prescription rates continued to increase for adults 60 years of age and over, and suicide rates continued to decrease.[32]

Antidepressant Pharmacotherapy and Suicidal Behaviour – Randomised Controlled Trials

As discussed above, the successful acute and long-term pharmacotherapy of unipolar depressives (sometimes in combination with anxiolytics, mood stabilisers and antipsychotics) reduces the risk of suicide attempts and completed suicide in the vast majority of patients. On the other hand, the meta-analysis of phase II/III randomised controlled clinical trials on antidepressant monotherapy on unipolar major depression, from which trials including the most severe and acutely suicidal patients are excluded (and therefore, no detectable antisuicidal effect could be expected), shows a non-significant increase in suicidal behaviour in patients taking antidepressants compared with those who are taking a placebo. Analysing the completed suicides on the basis of patient-years of phase II/III randomised controlled trials, it has been found that the annual rate of suicide was 0.6–0.9% with antidepressants and 0.3–0.5% with placebo.[5,7,19,20,33]

In a recent meta-analysis of 702 randomised controlled trials that included more than 87,000 depressive and other psychiatric patients, Fergusson et al.[14] found a significant increase in suicide attempts for patients taking SSRIs compared with placebo (odds ratio [OR] 2.28). However, when looking at the completed suicides, they did not detect any significant difference between SSRIs and placebo patients. The analysis of 25 outpatient paediatric antidepressant trials, that included more than 4,000 patients showed that 3.2% of the children taking antidepressants became 'suicidal' compared with 1.7% of those taking placebo, but again no patient in these antidepressant trials actually committed suicide.[22]

The interpretation of different suicide rates of major depressives taking SSRIs, older antidepressants and placebo in randomised controlled trials is sometimes very controversial. A meta-analysis of suicidal behaviour in terms of the absolute numbers of patients in a sample of six phase I–III randomised controlled FDA antidepressant trials (number of patients: 14.292)[34] reported that there were 225 patients with suicidal events (36 suicides and 189 attempts). The combined rate of suicides and attempts among patients on active antidepressants and on placebo were 1.55, 0.79 and 0.48%, respectively, suggesting a two- to three-fold higher risk of suicidal behaviour in patients on SSRIs and other antidepressants compared with patients taking placebo. However, the re-analysis of these data[19] showed that the rate of suicidal behaviour of SSRI trial placebo patients (0.66%) and the non-SSRI trial placebo patients (0.23%) also had a three-fold difference, seriously questioning the main conclusions of that meta-analysis. In addition, since patients on placebo-controlled trials usually spend a shorter time taking a placebo than the active drug (i.e. the drop-out rate for placebo patients is always higher), the analysis of suicidal behaviour in terms of absolute numbers of the patients results in a strong bias against active compounds.

Since severely ill co-morbid and actively suicidal patients, who are at the highest risk of manifesting suicidal behaviour,[2,3] as well as Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnosed bipolar I and bipolar II depressives, are excluded from antidepressant studies, randomised controlled trials are not suitable to rely on and conclude on any possible relationship between antidepressant use and the emergence of suicidal behaviour. The most interesting paradox of contemporary psychiatry is that antidepressants prevent suicidal behaviour among severely ill and frequently suicidal 'real-life' unipolar depressives,[4,13,16–18] but sometimes can provoke such behaviour in less severe, actually non-suicidal 'trial-life' unipolar depressives. The actual clinical condition of the patients at the time at which they become suicidal while taking antidepressants is usually an activated state that has been well-known for several decades ('increasing activity before improvement of mood'). However, recent findings strongly suggest that this relatively small increase in suicidality could be related to a depression-worsening potential of antidepressant monotherapy (when unprotected by mood stabilisers or atypical antipsychotics) in depressives with sub-threshold bipolarity (in clinical trials) and in unrecognised bipolar depressives (in real-life situations). When antidepressants worsen depression in a few patients, its psychopathological substrate might well reside in an agitated, excited, mentally overstimulated, anxious (bipolar) depressive mixed state.[21,35,36]

Recently, data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial put forward the possibility of a genetic vulnerability predisposing to the manifestation of new suicidal ideation after antidepressant treatment. This vulnerability might relate to ionotropic channels regulating glutamate activity and lead to suicidality through the behaviour analogue of anger.[36–38]

It should also be noted that in a clinical psychotherapy trial that enrolled adolescent outpatients with major depression similar to those enrolled in

antidepressant clinical trial rates of newly emergent suicidality in patients receiving only psychotherapy were comparable (i.e. somewhat higher) to those observed in antidepressant trials.[39]

Conclusion

Suicidality is one of the most alarming signs or symptoms in psychiatry and it is the most frequent source of medical contact in patients with mood disorders. The findings of current clinical research clearly indicate that successful treatment of unipolar major depression reduces suicide morbidity and mortality even in this high-risk population. Considering all of the above, psychiatrists must always be vigilant of the risk of suicidality when prescribing antidepressants (or implementing psychotherapy) to patients with depressive disorders where the risk of suicidal behaviour is inherently extremely high. There is evidence that concurrent depression-focused psychotherapies also increase the effectiveness of pharmacotherapy, and this may contribute to suicide prevention for patients with severe, recurrent unipolar major depression.[40] ■

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Depression is a major health problem which impairs psychosocial and occupational functioning, and is associated with significant morbidity and mortality. In the 2004 Global Burden of Disease Study, depression was found to be the third leading cause of burden of disease worldwide and the top leading cause of burden of disease in middle and high income countries.* Likewise, depression is a major health problem in Singapore, with the 2010 Singapore National Mental Health Survey reporting a 6.3% lifetime prevalence of depression in the Singapore adult population. The first edition of the MOH clini Successful treatment of depressed patients with antidepressants includes educating the patients and the families about available treatment options, time to onset of response and noticeable signs of it, early side effects and what to do about them, and the expected course of treatment. World J Biol Psychiatry Downloaded from informahealthcare.com by Prof. Siegfried Kasper on 08/30/13 For personal use only. Executive summary of recommendations. General recommendations. For patients who meet diagnostic criteria for depres-sive episode (ICD-10) or major depressive disorder (DSM-IV-TR), biological The suicide mortality can be further reduced by regular attendance in a specialised mood disorder clinic. View. Show abstract.Â Swedish statistics on suicide, use of antidepressants, unemployment and alcohol consumption were obtained for 1978-96. Time-series of the latter variables were compared with suicide rates. Demographic subgroups regarding age, gender and county were analysed. Suicide rates were also compared with the use of antidepressants in Denmark, Norway and Finland. Suicide rates decreased in accordance with the a priori hypothesis.Â Effects of Antidepressant Medication on Morbidity and Mortality in Depressed Patients After Myocardi January 2006 Â· Yearbook of Cardiology. B.J. Gersh.