



Why Has the Antidepressant Era Not Shown a Significant Drop in Suicide Rates?*

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1. Did Antidepressants Reduce the Suicide Rate? Negative Results

Depression is considered to be a major suicide precursor: An estimated 50% of those who die through suicide have suffered from depression (Isometsä et al., 1998). Among those ever hospitalized for depression the percentage who will die by suicide is estimated to be 15–19% (Guze & Robbins, 1970; Goodwin & Jamison, 1990). Lower figures are reported for depressed outpatient populations (Bostwick & Pankratz, 2000). The rate of attempted suicide in depression, though not exactly known, is much higher.

A major strategy in the treatment of depression, both major depression and dysthymia, is the prescription of antidepressant drugs. The use of those drugs has risen substantially over the years. In The Netherlands, for instance, the increase was 12% yearly over the past 4 years. Of course, antidepressants are also used in other conditions, but depression still remains the main reason for their prescription.

Rightly, then, one may expect suicide rates to have gone down, in proportion. This, however, did not happen. Suicide rates differ considerably from country to country and from region to region (Diekstra, 1995). Allowing for that, in most countries the rates of completed suicide seem to be quite stable. In The Netherlands, for instance, the number is approximately 1500 per year, for many years now. In some countries the suicide rate among males between 15 and 24 years of age has even increased (Lester & Yang, 1998). Overall rates of suicide attempts are not known, but in certain delineated areas they have tended to rise rather than to fall (Hawton et al., 1997).

Surely, the latter observation should not be generalized. An international study comparing rates of suicide attempt in 16 different European regions showed that those figures

varied from year to year and from region to region (Kerkhof, 2000). In some regions the frequency increased slightly between 1989 and 1992, whereas in others a likewise small reduction was observed. A robust and overall decline in the rate of attempted suicide, however, could certainly not be demonstrated.

Furthermore—and rather alarming—Khan et al. (2000) reported that rates of suicide and attempted suicide did not significantly differ in depressed patients treated with either placebo or an antidepressant. They analyzed studies with seven new antidepressant drugs, (i. e., fluoxetine, sertraline, paroxetine, venlafaxine, nefazadone, mirtazapine, and bupropion) using the USA Food and Drug Administration database. The study encompassed 19,639 patients. Annual rates of suicide and attempted suicide were 0.4% and 2.7% with placebo, 0.7% and 3.4% with active competitors (i. e., imipramine, amitriptyline, and trazadone), and 0.8% and 2.8% with the investigational drugs. In an analysis of studies carried out with venlafaxine ER and citalopram with a total of 23,201 patients comparable data were obtained (Khan et al., 2001).

In analyses of 77 studies with antidepressants, carried out in The Netherlands between 1983 and 1997 and encompassing 12,246 depressed patients, similar conclusions were reached: Suicide attempt rates did not differ significantly between placebo and experimental groups. These studies were part of a registration dossier of the Medicines Evaluation Board, the regulatory authority of The Netherlands (Storosum et al., 2001).

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2. Did Antidepressants Reduce the Suicide Rate? Positive Results

Controlled studies into the impact of antidepressants on suicide risk are scarce, but some of those have reported positive effects (Beasley et al., 1991). Selective serotonin reuptake inhibitors (SSRIs) were found to be superior in this respect to “broad spectrum antidepressants” (Montgomery et al., 1995). Others, however, failed to find such differences (Malone & Moran, 2001).

Yet, the relevant studies are unconvincing. They do not allow conclusions about possible beneficial effects of antidepressants on suicide rates, and this for several reasons. It concerns generally short-term studies with a limited number of patients. To demonstrate statistically that antidepressants produce an antisuicidal effect one needs, according to Isacson et al. (1996), at least 20,000 depressed patients randomly treated with either antidepressants or placebo. The studies reporting positive effects, however, were relatively small and not placebo-controlled. They were, moreover, not controlled for help-seeking behavior. Hence, it is conceivable that the positive results in the antidepressant groups—relative to the untreated groups—is the result of a greater propensity to seek professional help in times of mounting stress.

Finally, one has to keep in mind that serious suicidality is usually an *exclusion criterion* in placebo-controlled, therapeutic studies with antidepressants. This makes it hard to draw conclusions on the impact they may have exerted on suicidality.

Based on the data derived from a pharmaco-epidemiological study including Sweden’s entire population, Isacson et al. (1996) concluded that the application of antidepressants had indeed reduced the risk of completed suicide 1.8 times, relative to depressed patients not using antidepressants. The study, however, comprised no placebo-treated group. It is unclear, moreover, whether, and if so what kind of, nonpharmacological, particularly psychological, interventions had been practiced and whether both groups differed in that respect. Hence, the conclusions drawn by Isacson et al. (1996) seem to me premature. They themselves consider that conclusion to be strengthened by the observation that, parallel to an increase in prescription rate of antidepressants since the 1970s, the suicide rate has declined. However, in the past decades both doctors and patients became increasingly more aware of what depression is and how to treat it. This led to earlier diagnosis and more intensive treatment. In this period, moreover, new and effective psychological intervention techniques have been developed. They are employed with or without antidepressants. Therefore, it is not justified to pass the observed reduction of suicide rates simply to the credit account of antidepressants.

Patients with personality disorders, in particular those categorized as borderline patients, constitute another patient group with an increased suicide risk, for whom anti-

depressants are a therapeutic option. Few placebo-controlled studies have been published on the effect of antidepressants on suicidality and aggression regulation in this group of patients. They concern particularly the SSRIs. According to Coccaro and Kavousi (1997), outward-directed aggression responds favorably. Verkes et al. (1998) studied the effect of paroxetine vs. placebo in 91 suicidal, nondepressed patients with personality disorders, mainly of the borderline type. The study extended over a period of a year. In the group as a whole, paroxetine had no effect on the rate of suicide attempts. In the subgroup of patients who had attempted suicide five times or more in the previous years, paroxetine, however, did reduce the number of suicide attempts significantly. These data await confirmation and further exploration.

Taking all these data together, I arrive at the conclusion that one can advance only few and rather weak arguments to relativize the results of Khan et al. (2000, 2001) and Storosum et al. (2001). Their conclusions seem quite inescapable. The effect of ample use of antidepressants on suicide rates has been unimpressive, to say the least. Instead of disqualifying those data—like Quitkin and Kline (2001) tried to do with the first study of Khan’s group—or to disregard them, it seems wiser to raise the question: How come? Some possible explanations are discussed below.

3. Coincidence

Depression and suicidality are unrelated states. Their co-occurrence is a matter of coincidence, and hence it is not to be expected that suicide rates will be affected by treatment of depression.

This is not a likely explanation. First, because in that case one would expect suicidality to occur as frequently in the depressed as in the remitted state, and this is not the case. Suicide risk is to a high degree state-dependent and by far the greatest during a depressive episode (Roy, 2001). Psychopharmacological data, moreover, render it unlikely that depression and suicidality are disconnected. Montgomery et al. (1994), for instance, found that the SSRI fluoxetine is ineffective in brief recurrent depression, both with regard to depression and to suicidality.

Second, experiential data are contradictory. Depressed patients themselves generally experience a strong connection between feelings of hopelessness and suicidal tendencies.

Experiential data have substantial evidential power in psychiatry. The observation that suicide risk correlates stronger with feelings of hopelessness, as measured with the Beck scale, than with depression as such is a case in point. Hopelessness, moreover, may occur independent of depression or to a degree discrepant with depression severity (Mann et al., 1999).

Experiential, i. e., subjective, data are not held in high esteem in today’s research circles, preoccupied as they are

with objective assessment of data that can be established with a fair degree of objectivity. Subjective data are conceived as “soft,” because they are alleged to be not measurable reliably and reproducibly. This view is prejudiced (Van Praag, 1992). Methods are available to measure and to follow-up, prospectively and in a systematic and careful way, individual mood states and related cognitions. I am alluding to the *experience sampling method*. Although, regrettably, so far used only sparingly, it produces results that underscore the diagnostic importance of subjective psychopathology (Van Eck et al., 1998; Myin-Germeys et al., 2001). There is no convincing justification for neglecting substantial domains of psychopathology simply because they are subjective (Van Praag, 1992, 1997).

4. Continuity of Treatment

Continuity of treatment is not well looked after in patients with recurrent unipolar depression, even if their history records suicide attempts. Only 17% of a group of patients with major depression was prescribed antidepressant medication one month after a suicide attempt (Suominen et al., 1998). For many patients with recurrent depression it appears to be difficult, moreover, to take medicines faithfully over long periods of time.

It is thus conceivable that the small effect antidepressants have had on suicide rates is because of discontinuity of treatment: the result of misconceptions of the doctor or the lack of perseverance on the part of the patient. This explanation shifts responsibility from the remedy to the consumer and/or prescriber. If correct, *education permanente* of both parties should receive top priority.

It is, however, improbable that this conjecture holds good for the data of Khan et al. and Storosum et al. referred to above. They are derived from controlled trials, and in those studies strict control of medication intake generally got full attention.

5. Efficacy of Antidepressants

Antidepressants may be less effective than is generally accepted. If so, one cannot expect antidepressant treatment to have a major impact on suicidality, being frequently a complication of the depressed state. Indeed, many studies over the past 20 years showed generally modest effect size when comparing placebo and antidepressant drugs. A case in point is the study of Khan et al. (2000) cited above, reporting symptom reduction of 40.7% with investigational drugs, 41.7% with active comparators, and 30.9% with placebo. In a meta-analysis of 33 antidepressant trials Bollini et al. (1999) found an average improvement of 53% versus 35% in the placebo arms. The initial findings with antidepressants in the 1960s and 1970s were much more encouraging, reporting at least 30–35% placebo/drug differences (Van

Praag, 1978). If one is not satisfied with the easiest (but unsatisfactory) way out by declaring those data antiquated and invalid, then—once more—the question can be posed: how come? I will discuss a few possible explanations.

5.1 Blurring of Syndromes and the Neglect of Psychogenesis

Before the introduction of the DSM-III, diagnosis in psychiatry was, to be sure, not standardized, but it *was* detailed, at least in Western Europe. Two philosophies were dominant at the time: phenomenology and psychoanalysis. The first required precise accounting of symptomatological and experiential data; the second a detailed analysis of developmental factors possibly or supposedly involved in the etiology of the disorder.

With the introduction of the DSM-III, syndromal differentiation became a thing of the past. Symptomatologically, one qualifies for a particular diagnosis if *x* out of a series of *y* symptoms are demonstrable, irrespective of which ones. One diagnostic category, for instance, major depression or dysthymia, therefore covers a variety of syndromes. This approach has severely compromised diagnostic acuity. It is presently impossible to establish whether a particular antidepressant is preferentially effective in a particular depressive syndrome. Yet there are strong indications that those preferences do exist. Tricyclic antidepressants, for instance, were shown to be more helpful in endogenous than in nonendogenous depression (Van Praag, 1962; Heiligenstein et al., 1994; Roth, 2001).

If, in the study of antidepressants, presumably responsive and less- or nonresponsive patients are lumped together, the effect size of the drug will drop and approach the placebo response.

In the DSM classification, furthermore, the concept of psychogenesis all but disappeared. Axis I and Axis II disorders are registered independently. An assessment—hypothesis if you so will—of the relationship between developmental adversity and personality deviations on the one hand, and axis I diagnosis on the other, is no requirement. A quintessential issue in psychiatric diagnosing is disregarded. With that the role of psychotherapy in the treatment of depression declined, which might have diminished the therapeutic yield of antidepressant drugs (see 5.3 below).

The DSM system brought a standardization of psychiatric diagnosis, but also considerable impoverishment (Van Praag et al., 1987; Van Praag, 1992).

5.2. Border Problems

In recent years more and more subjects with depressive symptoms have been marked as candidates for treatment with antidepressants. The border between distress and depression, between worrying and a true mood disorder, how-

ever, is ill-defined (Van Praag, 2000). Distressed people and worriers cannot be expected to respond to antidepressant drugs. If an experimental group is made up of depressed and distressed individuals the response rate obtained with an antidepressant will be low and presumably lower than if only people with "case depression" had participated. An analogy: If one aspires to explore the efficacy of antibiotics in pneumonia one should guard against inclusion of patients with a common cold in the experimental group. This would result in underestimation of their therapeutic potential.

5.3. Stepchild Psychotherapy

The excessive confidence in the therapeutic power of psychological methods in treating depression, prevailing in the 1960s and 1970s, has been offset by a heavy reliance on antidepressant drugs as monotherapy, i. e., not in conjunction with psychotherapy. This might explain disappointing results obtained with antidepressants alone. Mood disorders frequently occur in subjects with personality disorders or deviant personality traits (Van Praag et al., in press). Personality frailties may play an important role in the etiology of mood disorders. Personality imperfections do not generally respond to antidepressants, but require psychological interventions. It is known, moreover, that personality disorders diminish the efficacy of antidepressants in depression (O'Leary & Costello, 2001). Exclusive reliance on antidepressants alone, at the expense of additional psychological interventions aimed at ego strengthening and defence intensification, will inevitably reduce the therapeutic return.

6. Residual Symptoms

In a substantial proportion of depressed patients treatment with antidepressants does not result in full recovery: residual symptoms persist (Fava, 1999; Agosti et al., 1993; Faravelli et al., 1986). Those can be true remnants of the depressive syndrome or manifestations of disappointment that treatment has been less successful than was hoped for. In this way suicidal tendencies might be maintained or triggered.

7. Personalities Traits

Depression and personality deviations often occur together (Hirschfeld et al., 1983; Clayton et al., 1994). Stress, produced by traumatic events or situations together with inadequate coping skills, is probably an important etiological factor in many cases of depression (Van Praag et al., in press). Suicidality, thus, might be not so much a feature of depression as such, but rather a consequence of preexisting personality traits. Personality pathology shows generally

little or no response to antidepressants, so that one cannot expect antidepressants to do suicidality much good.

Suicidality does indeed occur in nondepressed, personality-disordered individuals. This speaks in favor of this hypothesis. On the other hand, if personality pathology were the major cause of suicidality in depression, one would expect suicidal behavior to occur as frequently in depressive episodes as in states of remission—and this is not what actually happens.

8. Social Factors

Suicide rates have dropped because of antidepressants, but this effect might have been counterbalanced by the impact of social factors. This is a conceivable explanation. Socio-economic environment and prevalence of depression and suicidality are clearly associated (Hawton et al., 1988; Gunnell et al., 1999). In a small geographic area in Bristol (UK), for instance, Gunnell et al. (2000) found that social deprivation had risen over a period of 30 years, as had suicidal behavior. The relationship reached a statistically significant level. The social deprivation index was based on the sum of Z-scores of four variables: unemployment, car ownership, household overcrowding, and house ownership. Hence, it is conceivable that social factors have overridden the beneficial effects of antidepressants on suicide rates.

It is however unlikely that social deprivation occurred on such large scale in the developed world that it could explain why antidepressants have had such meager effects on suicidal behavior.

9. Have Antidepressants Increased Suicide Rates?

Antidepressants might have boosted suicidal impulses, cancelling out possible positive effects on depression per se. First, they could have energized an anergic patient before mood elevation had commenced and thus advanced, temporarily, the drive to harm or destruct oneself. This happens sometimes in the early phases of electroconvulsive treatment. The same could happen with antidepressants, particularly if they exert a pronounced stimulating effect on motoricity and level of initiative. Some evidence supports this notion (Damluji & Ferguson, 1988).

Another possibility is that antidepressants enhance the suicidal drive directly. A decade ago, a stir was caused by a publication claiming that fluoxetine, a selective serotonin reuptake inhibitor (SSRI), might increase suicidality in depression (Teicher et al., 1990). The meta-analysis of a large number of studies, however, could not confirm those conclusions. (For review see Healy, 1994; Fava & Rosenbaum, 1991; Beasley et al., 1991). Yet, this notion recently popped up again, when Healy (2000) reported that suicidal tenden-

cies had acutely occurred in a few normal subjects during treatment with the SSRI sertraline.

Theoretically, an influence of SSRIs on the regulation of (auto)aggression is certainly conceivable. Both in animals and in humans serotonin (5-hydroxytryptamine, 5-HT) systems are associated with the regulation of (auto)aggression. Most notably, the 5-HT_{1A} and 5-HT_{1D} receptor-mediated systems are involved. Increasing activity in those neuronal systems will inhibit and decreasing activity will enhance (certain forms of) aggression (Olivier & Mos, 1992).

The 5-HT receptors mentioned are located both pre- and postsynaptically. Activation of the postsynaptic receptor leads to activation of the system; activation of the presynaptic counterpart to reduced activity in the system.

The immediate effect of an SSRI is to increase availability of 5-HT in the synapse and stimulation of both pre- and postsynaptic 5-HT_{1A} and 5-HT_{1D} receptors. The net effect on 5-HT-ergic activity will thus be small because pre- and postsynaptic effects generally cancel each other out. After some time (weeks) SSRIs desensitize the presynaptic 5-HT_{1A} receptor. (It is unknown whether this is also the case with the 5-HT_{1D} receptor.) This does not happen with the postsynaptic counterpart (Blier & De Montigny, 1994). In this way the 5-HT_{1A} system gets activated, and this effect is considered crucial for antidepressant activity. It is, as said, also associated with reduced aggressivity.

If, for whatever reason, during a certain period, activation of the presynaptic 5-HT_{1A} (and/or the 5-HT_{1D}) receptor outstrips activation of the postsynaptically located 5-HT_{1A} receptor, causing a reduction of neuronal activity in the 5-HT_{1A} system, depressive behavior might theoretically be intensified and (auto)aggressive impulses accentuated, with suicidality as a possible result.

This possibility, however, is for the time being speculative; it has not been demonstrated and would be hard to demonstrate in humans.

10. Conclusions

Taking into account that depression is a major suicide precursor, and that over the past 20 years antidepressants have been employed on an ever-increasing scale, it is puzzling that suicide rates have not dropped accordingly. These observations should be taken seriously and studied systematically to discover the reason why. They should definitely not be swept under the rug because they do not fit consensus opinions about the treatment of depression prevailing in psychiatry today.

11. Summary

Over the past decades the rate of completed suicide has remained quite stable, whereas that of suicide attempts seems to have increased (to the extent it has been studied in defined regions). These are puzzling observations, since

depression is the major suicide precursor and and since antidepressants have been increasingly used over the years in the treatment of depression. These observations have not attracted sufficient attention, possibly because they do not accord with consensus opinions about depression treatment in psychiatry today. This paper discusses a number of possible explanations that not only deserve, but are definitely in need of systematic investigation.

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