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Suicide in the course of the treatment of depression

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Five different mechanisms have been proposed whereby antidepressant treatment might lead to suicide: first by simply ameliorating depressions more rapidly; second by an action intrinsic to the specific antidepressant effects; third by toxicity in overdose; fourth by side-effects of specific antidepressants; and finally by virtue of treatment inefficacy. Evidence from randomized control trials (RCT), controlled case studies and epidemiological studies on this question is reviewed and it is concluded that antidepressants can be implicated in some cases of suicide during treatment. Modifications of clinical trial methods and pharmacogenetic studies would yield a richer data set to explore this issue further.

Key words: akathisia; antidepressants; behavioural toxicity; case reports; suicide

Introduction

One of the first controversies of the psychopharmacological era concerned associations between psychopharmacotherapy and suicide. Although thought of as a neuroleptic, the only placebo-controlled randomized control trials (RCT) conducted with reserpine indicated that it was an antidepressant (Davies and Shepherd, 1955). A simultaneous series of reports in the *New England Journal of Medicine*, *JAMA*, the *BMJ* and the *Lancet*, however, implicated it in the precipitation of depression and suicide (see Healy and Savage, 1998). Despite early prominence, this issue has been comparatively neglected, perhaps because we do not wish to contemplate the possibility that useful treatments may on occasion be problematic. Nevertheless, there have been five distinct proposals as to how treatment might be associated with suicide and the problem of deciding what possibilities, if any, the evidence supports also raises a host of intriguing methodological issues.

Suicide on treatment: the mechanisms

Depression and suicide

Before the advent of the antidepressants, a number of authorities (Staehelin, 1955) had argued that depressed patients were likeliest to commit suicide when they were entering into or coming out of a depressive disorder. It followed that antidepressants, if they alleviated depressions without permanently correcting the underlying disease, would lead to more entries into and exits from depressed states. Suicide therefore had to be a risk of treatment and it occurred in the first studies of imipramine (Kielholz and Battegay, 1958).

Antidepressant effect and suicide

Kielholz later proposed that specific antidepressant actions might be associated with suicide. His initial impression was that the monoamine oxidase inhibitors (MAOIs), which he categorized as the most drive enhancing, were most associated with suicide attempts, followed by desipramine and nortripytline by virtue of alleviating depressive psychomotor retardation before they cleared up suicidal ideation (Kielholz, 1971). When the effects of these agents on monoamine systems were established, it appeared that there was a particular problem with antidepressants selective for catecholamine systems. A long-term maintenance study with maprotiline (Rouillon *et al*., 1989) in which there were five suicides and nine attempted suicides on maprotiline compared with one suicide in a smaller placebo group appeared to bear out this idea.

Antidepressant toxicity and suicide

In the 1980s, a debate developed about the relative toxicity of antidepressants in overdose. This centred on the safety of mianserin, which had been associated with agranulocytosis. The argument hinged on a calculus of risks and benefits. While mianserin might be associated with lowered white cell counts, its defenders argued that it was safer in overdose than other antidepressants and that therefore its use would be associated with a lower death rate overall (Pinder, 1988). This debate led to the construction of a fatal toxicity index based on the number of deaths following use of each antidepressant as a proportion of the number of scripts written (Cassidy and Henry, 1987; Pinder, 1988; Henry, 1992). When these calculations were made, desipramine, amitriptyline and dothiepin, which are more toxic in overdose than other antidepressants, appeared to be associated with more deaths. The implication was that there might be a public health gain by switching prescriptions to less toxic compounds.

Antidepressant side-effects and suicide

Against a background that catecholaminergic agents might be more likely to be associated with suicidality and the safety in overdose of the selective serotonin reuptake inhibitors (SSRIs), the next development came as surprise. A series of case reports

(Teicher *et al.*, 1990a,b,c; Creaney *et al.*, 1991; King *et al.*, 1991; Rothschild and Locke, 1991; Wirshing *et al.*, 1992; Healy, 1994) suggested that fluoxetine might induce suicidal ideation *de novo* in a proportion of vulnerable individuals by triggering an akathisic state. This was perceived by some as an attack on fluoxetine, although Teicher *et al.* (1991) and others (Healy, 1994) saw the problem in terms of a potential that all antidepressants might have through side-effects, such as akathisia or depersonalization (Damluji and Ferguson, 1988; Healy, 1994). One problem with such side-effects early in treatment may be a risk of misattribution by the patient to a worsening of their illness.

Antidepressant inefficacy and suicide

Another possibility was raised by Isacsson and colleagues (1994), who analysed all suicides in Sweden for 1990/1991. They found that lofepramine was least likely to be found in the bloodstream of suicides, the most commonly used tricyclics were intermediate in frequency and mianserin and moclobemide were the most commonly found agents. They introduced the argument that suicide might be associated with treatment inefficacy. In support of this idea, they noted two pieces of evidence. First, there was the relatively high rate of suicides on moclobemide and low rate for clomipramine and they noted that clomipramine had been shown in clinical trials to have a superior treatment effect size to moclobemide in severe depressions. Second, a range of studies (e.g. Isacsson *et al.*, 1994) suggest that completed suicides have sub-therapeutic blood levels of antidepressants.

Suicide on treatment: methodological issues

An association between antidepressant treatment and suicide raises complex issues of causality given that depression itself is closely associated with suicidality. Depression, however, is also closely associated with sexual dysfunction and yet it has been possible to reach agreement on the existence of antidepressant-induced sexual dysfunctions. For some of the mechanisms outlined above, a causal relationship between treatment and effect (suicide) has face validity; other things being equal antidepressants that are safer in overdose should be associated with fewer deaths from suicide. For other issues, such as treatment inefficacy or the emergence of suicidal ideation, the picture is less clear. We explore these issues, using data from clinical trials, case reports and epidemiological studies, and focus on fluoxetine because the issues have been most keenly debated for this agent, although the same points apply to all antidepressants.

Clinical trials

Associations between fluoxetine and suicidality have been denied on the basis that RCTs are the only means to demonstrate cause and effect and that no trials with fluoxetine have shown the emergence of suicidality or akathisia (Beasley, 1991; Nakielny, 1994). In an era when evidence based medicine is in favour and RCTs are held up as the best form of evidence, this argument carries considerable weight. There are, however, a number of problems with the notion that RCTs are a necessary means to establish cause and effect or the best means in all circumstances.

Clinical trials and suicide

A considerable amount of work has now indicated that prior suicidality or baseline agitation need not be contra-indications to treatment with fluoxetine (Beasley *et al.*, 1991; Tollefson *et al.*, 1994). Indeed, independent studies suggest that SSRIs might be most effective in patients with borderline personality features, who might be expected to impulsively attempt suicide (Joyce *et al.*, 1994). An analysis of the fluoxetine database, looking at item 3 of the Hamilton Depression Rating Scale, indicated a fall in suicidality ratings in patients on fluoxetine comparable to that found with reference antidepressants and greater than found on placebo (Beasley *et al.*, 1991). It also demonstrated that a greater number of subjects showed item-3 increases on placebo (Beasley *et al.*, 1991). Similar findings have been reported for paroxetine (Montgomery *et al.*, 1995). Clearly, SSRIs including fluoxetine have a place in the management of depressive suicidality.

However, the use of RCTs by pharmaceutical companies is largely determined by registration requirements for evidence of some treatment effect. The patients recruited to such studies are samples of convenience, which need not represent either the general population or any vulnerable population within in it. These trials are not designed to answer the question of whether the drug on occasion can trigger an emergence of suicidality. To date, there have been no such trials. A meta-analysis of studies conducted for other purposes, using instruments that were never designed to settle this question is no substitute, given experimental indications showing patients and observers may fail to rate even intense newly emergent drug-induced suicidality (Healy and Farquhar, 1998). Quite simply, beneficial effects on suicidality in a majority of depressed patients do not outrule drug induced problems anymore than a reduction of pertussis induced brain damage outrules vaccine induced injuries.

Clinical trials and side-effects

The precise frequency with which SSRI-induced akathisia/nervousness occurs is uncertain, even though akathisia was reported very early as a side-effect of fluoxetine treatment (Lipinski *et al.*, 1989) and Ayd's (1996) *Lexicon for Psychiatry and Neurology*, states that 'fluoxetine's capacity to evoke akathisia is well recognized'. This is largely because few RCTs have been designed to establish the precise incidence of side-effects. Although not unconcerned about side-effects, regulators make judgements about primary treatment effects and on aspects of toxicity rather than on the frequency of side-effects.

In a poster review of the fluoxetine database involving 1610 fluoxetine patients and 952 placebo patients, Plewes *et al.* (1997) reported statistically significant differences between fluoxetine and placebo in rates for anxiety (12.1% versus 6.9%) and for nervousness (13.7% versus 8.8%). It can be objected that neither of these side-effects refer to akathisia. The problem here is that good clinical practice (GCP) advocates coding side-effects according to a WHO dictionary 'The International Monitoring of Adverse Reactions to Drugs Terminology' (1994). This is based on reports made by patients. Akathisia is not a word patients use. Accordingly

subjects who become subjectively akathisic must necessarily be reported under headings such as nervousness or anxiety. There is therefore a legitimate reason for not reporting akathisia but it is misleading to imply that it does not happen. Plewes *et al.* (1997) distinguish between nervousness and anxiety but, if these differ, it is difficult to see that one of them can refer to anything other than agitation/akathisia.

There is another aspect to side-effect reporting. To date, companies have only reported spontaneously mentioned side-effects, which are likely to be a small proportion of actual side-effects. Until recently, no patients were required to complete a comprehensive list of potential side-effects such as the UKU (Lingjaerde *et al.*, 1987). In the case of sexual dysfunction, early clinical trial estimates, based on spontaneous reporting, suggested a rate of 5% on fluoxetine (Stark and Hardison, 1985). Subsequent investigations with instruments sensitive to drug induced sexual dysfunction point to rates greater than 70% (Patterson, 1993). This clearly indicates how a problem can be completely missed if the means of investigation is inadequate. The situation is compounded by indications that some clinical trials are run by minimally supervised, untrained personnel, who are likely to be insensitive to the emergence of novel problems and issues (Stecklow and Johannes, 1997).

Case studies

Nevertheless, the argument goes that the Food and Drug Administration (FDA) would only register compounds on the basis of RCTs because only they, in contrast to case reports, can demonstrate causality. This is not true. Activated charcoal is licensed for overdoses with compounds such as strychnine on the basis of a single case, when Pierre Touery drank 10 times the lethal dose of strychnine and survived, having taken activated charcoal beforehand (Healy, 1997). The FDA's post-1962 statutes permit placebo-controlled trials, active comparator trials, historical controls as well as single cases to be used as the basis for a licence. The only requirement is that the procedure used has assay sensitivity. In the case of an anaesthetic, for example, falling asleep 30 s after a drug is given is so unlikely that independent observers could validly conclude on the basis of a single case that the drug had produced the treatment effect being claimed for it (Leber, 1998). Further studies would be required for registration purposes, in order to demonstrate the safety of the compound.

RCTs are needed when an expected treatment effect is relatively small or when there is spontaneous variation in the index condition or when the bias of investigators is likely to influence the results unless such controls are introduced. They are needed in the registration of antidepressants, where the treatment effect sizes of some antidepressants, relative to the spontaneous variation in milder depressions, is so small that upwards of 300 patients may be required to demonstrate significance. The emergence and resolution of akathisia is more visible and clearcut and less subject to spontaneous variation than the emergence and resolution of depression. It is rare naturally. Its occurrence following drugs is so well established that no one has ever called for an RCT to prove it although such a trial might establish the rate at which particular agents induce it.

Nevertheless, in case studies proposing an association between a clearcut treatment emergent event, like akathisia, and particular drugs there should be controls in the design. There are no controls built into associations between suicidality and antidepressants drawn simply from the spontaneous medical reports filed by individual practitioners and no credible case could be based on such reports. But case reports of this kind should not be confused with case studies, which have controls, such as a test–retest design, built into them. The results from test–retest designs can permit valid scientific conclusions to be drawn (Karch and Lasagna, 1977; Kazdin, 1982; Stephens, 1983; Girard, 1987; Beasley, 1991; Edwards, 1992; Jick *et al.*, 1992; Healy, 1994). Indeed, no less an investigator that Bradford Hill, the creator of the RCT, stated that RCTs were not the only way to assess drug effects (Hill, 1966). A test–retest design was employed by Rothschild and Locke (1991), Creaney and colleagues (1991) and Wirshing and colleagues (Wirshing *et al.*, 1991) when looking at the emergence of suicidal ideation on fluoxetine.

Another control was introduced by the eminence of the reporters. A further control stemmed from the fact that similar reports came from a wide range of independent investigators. The finding could not easily be explained in terms of the bias of one investigator or centre. Furthermore, in contrast to spontaneous medical reports, senior investigators agreed on the details of what was happening and in the Teicher series, six cases were described rather than just an isolated case, in the Wirshing series, five cases, and in the King series, a further six cases.

Finally, it is clear from reading these reports that senior investigators thought they were witnessing something different to the usual suicidal ideation that occurs in depression. There was a consistency across the reports as to what was happening, namely that suicidal ideation might be triggered by inducing akathisia/agitation. The argument therefore did not depend on an inexplicable association. It can also be noted that, at the same time, studies on suicide risk factors, conducted by the National Institute of Mental Health, pointed to levels of anxiety and agitation as the most significant predictors of completed suicides in the months following the commencement of treatment (Fawcett *et al.*, 1990; Fawcett, 1992).

Epidemiological studies

Another means to establish the impact of antidepressants on suicidality is to look at epidemiological studies. There are two studies relevant to the question of antidepressants and suicide (Jick *et al.*, 1995; Isacsson *et al.*, 1994). The Jick study, conducted in a primary care setting, looked at suicides following 172 000 antidepressant prescriptions. As dothiepin was the most commonly prescribed antidepressant in this sample, it was assigned a relative risk of 1.0, against which the risk came out at 2.1 for fluoxetine, 0.5 for lofepramine and 1.8 for mianserin. Translated into deaths per 100 000 patient years, the figure was 47 for lofepramine, 86 for dothiepin, 165 for mianserin and 189 for fluoxetine.

In the entire sample, the difference between dothiepin and fluoxetine was significantly different at 95% confidence intervals. When all confounding factors such as prior history of suicide attempt and antidepressant prescription were taken

into account, the best estimate of the relative risk of fluoxetine to dothiepin remained at 2.1, although the confidence interval — a function of sample size, which had been halved — changed. In contrast, when confounds were controlled for, the best estimate for mianserin, which had been widely promoted as being safe in overdose, fell from 1.8–1.1, suggesting that it but not fluoxetine was being prescribed to patients who were perceived to be at greatest risk.

Clearly, one study is of limited value but a number of points can be noted. First, this study refers to real life rather than to a sample of convenience. There are likely to be confounds but it is not clear what weight should be put on them. On the one hand, a proportion of imipramine prescriptions, for example, will have been given for enuresis and 10 year olds are unlikely to commit suicide. On the other hand, it is not possible to kill oneself by overdose with fluoxetine and it is likely therefore that there were a greater number of unrecorded attempted suicides from overdose with fluoxetine than there were for some other compounds. Furthermore, in keeping with an induction of akathisia, the deaths from violence on fluoxetine were proportionately higher than for other antidepressants. A further point is that before the study began it was widely accepted that lofepramine was one of the safest antidepressants, because of both its efficacy and safety in overdose, and the findings of the study confirmed this, which suggests that the study methodology was coming up with accurate results.

Finally, the Jick study does not stand in isolation. Isacsson and colleagues (1994) analysed all suicides in Sweden for 1990/1991 in a study that was larger in terms of completed suicides than the Jick study. They found the same rank ordering of suicides by antidepressant; lofepramine was the safest, the most commonly used tricyclics were intermediate and mianserin was the riskiest (fluoxetine had not then been licensed in Sweden), with an almost identical figure, 41 out of 100 000 patients/years, for lofepramine.

In addition to a low death rate on lofepramine, the other noradrenergic selective agent, maprotiline, was associated with a lower than average death rate. Combined these figures from two studies cast doubt on Kielholz's early proposal that drive enhancing antidepressants would be associated with suicides by virtue of a propensity to stimulate drive leaving suicidal ideation intact. There was a dissociation between these noradrenergic selective agents and moclobemide, however, which suggests that Kielholz's original perceptions that there might be a problem associated with MAOIs may need further consideration.

As regards the possibility that treatment inefficacy might be associated with suicide (Isacsson *et al.*, 1994), it is probably a mistake to think that treatment effect sizes are some absolute value (Healy, 1998). They only ever hold relative to specified populations, and certain populations such as patients with obsessive–compulsive disorder or adolescent depressions, who might be expected to do better on SSRIs than tricyclic antidepressants, may be inherently less likely to commit suicide. It is not clear therefore that demonstrations of greater treatment effect sizes for some antidepressants in severe depression (Wheatley *et al.*, 1998; Lopez-Ibor *et al.*, 1996) will necessarily translate into benefits in terms of reduced suicides.

Epidemiology in the public domain

In the debate about suicide and depression, a 15% lifetime suicide risk for depression is invariably cited (Guze and Robins, 1970) or a 79-fold increase in rate compared with the normal population (Hagnell *et al.*, 1981). Against such a background it is suggested that it is impossible to determine if an antidepressant causes suicide. Inskip and colleagues (1998) have updated estimates for lifetime suicide risks for affective disorders, citing a figure of 6%. However, both this and Guze's estimates are drawn almost exclusively from populations of severe and hospitalized depressives. The lifetime suicide risk for mild to moderate depressive disorders is not known but it can be modelled. Current estimates of lifetime affective disorder prevalence have risen to between 30% and 50% of the population (Hagnell *et al.*, 1981; Blacker and Clare, 1987; Kessler *et al.*, 1994). Given that the population of England and Wales is 50 million with 5000 suicides per annum, if half of the suicides are affective disorder related (2500), multiplying by 75 (an average life expectancy) and dividing by 12.5 million (25% lifetime prevalence) gives a lifetime suicide risk of approximately 1.5% for all affective disorders. A possible conclusion from this exercise is that it makes little sense to talk about a global lifetime risks of suicide for affective disorders and more sense to talk about suicide risks for severe, moderate and mild affective disorders, which might approximate to 15%, 6% and 1–1.5%, respectively.

If the annual prevalence of affective disorders is 10% (Blacker and Clare, 1987; Kessler *et al.*, 1994) and depressions account for 50% of suicides, this gives a figure of 50 suicides per 100 000 patient years for all affective disorders. Stripping out figures for severe depressive disorders suggests that annual suicide rates for mild affective disorders are probably no more than 25–40 suicides per 100 000 years. These figures offer no room for complacency when set against the Jick and Isacsson figures,.

Conclusions

The data from the variety of sources quoted here present a complex picture from which simple conclusions are not readily drawn. By virtue of the variation between agents found in the studies of Cassidy and Henry, Jick and colleagues and Isacsson and colleagues, it is all but impossible not to accept that antidepressant treatment in a small proportion of vulnerable patients may be linked causally with death by suicide. This statement however, does not mean that antidepressant treatment increases the overall rate of suicide. The situation resembles that with pertussis vaccination and brain damage where overall levels of brain damage may fall after vaccination yet particular children may be adversely affected by the vaccine. The example of reserpine is relevant here. The suicides with which it was associated came from non-depressed hypertensive populations and were probably triggered by akathisia (Healy and Savage, 1998). This demonstrates the ability of a psychotropic agent to lead to the emergence of problems that cannot be easily passed off as stemming from an underlying psychiatric disorder, as do healthy volunteer studies (Healy and Farquhar, 1998).

There appears therefore to be a case that psychotropic agents can make vulnerable individuals worse while benefiting

the population at large. It can be noted that psychotherapy has been associated with increased rates of suicide on a population rather than individual basis (Moller, 1992; van der Sande, 1997). Arguments that suicides happen in the young schizophrenic seized with a flash of insight at the awful prospects ahead of them or the depressed patient with drive restored but suicidal ideation intact put little onus on the clinician. This review suggests that things may not be so simple. Clearly, bearing in mind the toxicity of certain agents in overdose is one thing but there appear to be other things they can do as well.

The subjective dysphoria that antipsychotics and antidepressants may produce remains poorly characterized. At present there is no agreement on what the overlap may be between subjective akathisia and drug induced dysphoria (Sachdev, 1995; Healy and Farquhar, 1998). Such reactions can, however, lead remarkably quickly to depressive, suicidal and violent thoughts even in healthy individuals (Healy and Farquhar, 1998). There is a need to investigate these issues more thoroughly, given the role that akathisic reactions appear to have played in this story right from the earliest use of reserpine.

Given the present state of clinical trials, the role that such reactions may play in causing problems is best teased out by means of test–retest methods. That this is the case is attested to by senior clinical trialists such as Lasagna (Karch and Lasagna, 1977), epidemiologists such as Jick, pharmaceutical company investigators such as Stephens of Glaxo (Stephens, 1983), Girard of Synthelabo (Girard, 1987), Beasley of Eli Lilly (Beasley, 1991) and others. If data from clinical trials are to play a greater part in informing the debate, there is a twofold need. One is for trials designed to specifically address the issue. The other is for a more comprehensive and less discretionary recording of the adverse effects of treatment. This might be achieved by incorporating mandatory self-ratings of side-effects using instruments such as the UKU.

As regards lessons to be learned from the current dataset, it appears that antidepressants selective to noradrenergic systems do not pose problems to the extent that was once proposed, although paradoxical worsening of depression on these agents has also been noted (Damluji and Ferguson, 1988). The picture as regards the MAOIs remains less certain. There seems some possibility that at least one SSRI, fluoxetine, may be associated with higher rates of suicidality in certain individuals. It remains unclear whether this is a problem likely to affect all SSRIs or only those SSRIs used in particular populations. If akathisia is the mechanism by which this effect is mediated, then this is a problem that can be minimized by prescribers being aware of the possibility and advising patients accordingly.

It should be noted that other side-effects, such as depersonalization or urinary retention, mediated through other systems, also have the potential to cause problems. The entire area of distress induced by adverse events and strategies to minimize these problems is deserving of further investigation. It is opportune to raise the issue of antidepressant induced suicidality when the possibility of greatly minimizing such reactions has now emerged. From the early 1960s, there were good pharmacogenetic indications that some individuals responded preferentially to MAOIs while others responded to serotonin reuptake inhibiting tricyclic agents (Pare *et al*., 1962). Similar indications emerge from the fluoxetine and akathisia data. There would therefore seem to be some pharmacogenetic basis for adverse responses to selective agents. Clinical, scientific and other considerations all suggest that this area should be the focus of intense development.

If it is conceded that antidepressant treatment in some instances can cause problems, there is a separate public health question as to how this should impact on national programmes to reduce the incidence of suicide by enhancing the detection and treatment of depression. For moderate to severe depressive disorders, there are good indications that detection and treatment reduce suicide rates (Rutz *et al*., 1995). Furthermore, Isacsson *et al*. (1994) suggested that a greater number of depressives died from suicide because they were not treated than may have died because of the adverse effects of any particular antidepressant. Finally, better detection and treatment of depression in Sweden during the 1980s was possibly associated with a national decline in suicide rates (von Knorring and Bingefors, 1998). Pharmacotherapy may also have benefits across diagnostic categories. It will clearly reduce suicide rates in schizophrenia and probably also in some personality disorders (Montgomery and Montgomery, 1982).

The picture is less certain for milder affective disorders, where it remains unproven that lifetime prevalences for suicide can be reduced. In such circumstances, detection and treatment trials are clearly warranted but there is an increasing onus on prescribers and companies to acquaint themselves with the hazards of treatment, to inform the patient on how to handle these and to monitor the impact of treatment.

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References

Ayd F Jr (1996) Lexicon for psychiatry, neurology and neuroscience, p. 268. Williams & Wilkins, Baltimore

Beasley C (1991) Fluoxetine and suicide. BMJ *303*: 1200

Beasley C M, Dornseif B E, Bosomworth J C, Sayler M E, Rampey A H, Heiligenstein J H, Thompson V L, Murphy D J, Masica D N (1991) Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ *303*: 685–692

Blacker R, Clare A (1987) Depressive disorder in primary care. Br J Psychiatry *150*: 737–751

Cassidy S L, Henry J A (1987) Fatal toxicity of antidepressant drugs in overdose. BMJ *295*: 1021–1024

Creaney W, Murray I, Healy D (1991) Antidepressant induced suicidal ideation. Hum Psychopharmacol *6*: 329–332

Damluji N F, Ferguson J M (1988) Paradoxical worsening of depressive symptoms caused by antidepressants. J Clin Psychopharmacol *8*: 347–349

Davies D L, Shepherd M (1955) Reserpine in the treatment of anxious and depressed patients. Lancet 117–120

Edwards G (1992) Antidepressants and murder. Psychiatr Bull *16*: 537–539

Fawcett J, Scheftner W A, Fogg L, Clark D C, Young M A, Hedeker D, Gibbons R (1990) Time-related predictors of suicide in major affective disorders. Am J Psychiatry *147*: 1189–1194

Fawcett J (1992) Suicide risk factors in depressive disorders and in panic disorder. J Clin Psychiatry *53*: 9–13

Girard M (1987) Conclusiveness of rechallenge in the interpretation of adverse drug reactions. Br J Clin Pharmacology *23*: 73–79

Guze S, Robins E (1970) Suicide and primary affective disorder: a study of 95 cases. Br J Psychiatry *117*: 437–438

Hagnell O, Lanke J, Rorsman B (1981) Suicide rates in the Lundby study: mental illness as a risk factor for suicide. Neuropsychobiology *7*: 248–253

Healy D (1994) The fluoxetine and suicide controversy. CNS Drugs *1*: 223–231

Healy D (1997) The antidepressant era. Harvard University Press, Cambridge, MA

Healy D (1998) Meta-analysis of trials comparing antidepressants with active placebos. Br J Psychiatry *172*: 232–234

Healy D, Farquhar G N (1998) Responses to droperidol in healthy volunteers. Hum Psychopharmacol *13*: 113–120

Healy D, Savage M (1998) Reserpine exhumed. Br J Psychiatry *172*: 376–378

Henry J A (1992) The safety of antidepressants. Br J Psychiatry *160*: 439–441

Hill A B (1966) Reflections on the controlled trial. Ann Rheum Dis *25*: 107–113

Inskip H M, Harris E C, Barraclough B (1998) Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry *172*: 35–37

Isacsson G, Holmgren P, Wasserman D, Bergman U (1994) Use of antidepressants among people committing suicide in Sweden. BMJ *308*: 506–509

Jick H, Ulcickas M, Dean A (1992) Comparison of frequencies of suicidal tendencies among patients receiving fluoxetine, lofepramine, mianserin or trazodone. Pharmacotherapy *12*: 451–454

Jick S, Dean A D, Jick H (1995) Antidepressants and suicide. BMJ *310*: 215–218

Joyce P R, Mulder R T, Cloninger C R (1994) Temperament predicts clomipramine and desipramine responses in major depression. J Affective Disorders *30*: 35–46

Karch F E, Lasagna L (1977) Towards the operational identification of adverse drug reactions. Clin Pharmacol Therapeut *21*: 247–253

Kazdin A (1982) Single-case research designs. Oxford University Press, New York

Kessler R C, McGonagle K A, Zhao S, Nelson C B, Hughes M, Eshleman S, Wittchen H U, Kendler K S (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Co-morbidity study. Arch Gen Psychiatry *51*: 8–19

Kielholz P, Battegay R (1958) The treatment of depressive states: with special reference to Tofranil, a new antidepressive. Schweizerische Medizinische Wochenschrift *88*: 763–767

Kielholz P (1971) Diagnose und Therapie der Depressionen fur Praktiker. JF Lehmanns, Munich

King R A, Riddle M A, Chappell P B, Hardin M T, Anderson G M, Lombroso P, Scahill L (1991) Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. J Am Acad Child Adolesc Psychiatry *30*: 171–176

Knorring von L, Bingefors K (1998) Resistant depression: the need for better antidepressants. In Briley M, Montgomery S (eds), Antidepressant therapy at the dawn of the third millennium, pp. 319–332. Martin Dunitz, London

Leber P (1998) Managing uncertainty. In Healy D (ed.), The psychopharmacologists, Vol. 2. Chapman & Hall, London

Lingjaerde O, Ahlfors U G, Bech P, Dencker S J, Elgen K (1987) The UKU side-effect rating scale. Acta Psychiatr Scand *76 (Suppl.)*: 334

Lipinski J F, Mallya G, Zimmerman P *et al.* (1989) Fluoxetine induced akathisia: clinical and theoretical implications. J Clin Psychiatry *50*: 339–342

Lopez-Ibor J J, Guelfi J, Pletan Y, Tournox A, Prost J F (1996) Milnacipram and selective serotonin reuptake inhibitors in major depression. Int Clin Psychopharmacol *11 (Suppl. 4)*: 41–46

Moller H-J (1992) Attempted suicide: efficacy of different aftercare strategies. Int Clin Psychopharmacol *6 (Suppl. 6)*: 58–69

Montgomery S A, Montgomery D B (1982) Pharmacological prevention of suicidal behaviour. J Affect Disord *4*: 291–298

Montgomery S A, Dunner D L, Dunbar G C (1995) Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. Eur Neuropsychopharmacol *5*: 5–13

Nakielny J (1994) The fluoxetine and suicide controversy. A review of the evidence. CNS Drugs *2*: 252–253

Pare C M B, Rees W L, Sainsbury M J (1962) Differentiation of two genetically specific types of depression by the responses to antidepressants. Lancet 1340–1343

Patterson W M (1993) Fluoxetine-induced sexual dysfunction. J Clin Psychiatry *54*: 71

Pinder R (1988) The risks and benefits of antidepressant drugs. Human Psychopharmacology *3*: 73–86

Plewes J M, Koke S C, Sayler M E (1997) Adverse events and treatment discontinuations in fluoxetine clinical trials: an updated meta-analysis. Eur Neuropsychopharmacol 7: S169

Rothschild A J, Locke C A (1991) Re-exposure to fluoxetine after serious suicide attempts by 3 patients: the role of akathisia. J Clin Psychiatry *52*: 491–493

Rouillon F, Phillips R, Serrurier D, Ansart E, Gerard M J (1989) Rechutes de dépression unipolaire et efficacité de la maprotiline. L'Encéphale *15*: 527–534

Rutz W, von Knorring L, Pihlgren H, Rihmer Z, Walinder J (1995) An educational project on depression and its consequences: is frequency of major depression among Swedish men underrated resulting in high suicidality? Primary Care Psychiatry *1*: 59–63

Sachdev P (1995) Akathisia and restless legs. Cambridge University Press, Cambridge

Staehelin J (1955) Über Depressionszustände. Schweiz Med Wochenschrift *85*: 1205

Stark P, Hardison C D (1985) A review of multicenter controlled studies of fluoxetine versus imipramine and placebo in outpatients with major depressive disorder. J Clin Psychiatry *46*: 53–58

Stecklow S, Johannes L (1997) Questions arise on new drug testing. Drug makers relied on clinical researchers who now await trial. Wall Street Journal 15 August

Stephens M (1983) Deliberate drug rechallenge. Hum Toxicol *2*: 573–577

Teicher M H, Glod C, Cole J O (1990) Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry *147*: 207–210

Teicher M H, Glod C, Cole J O (1991) Dr Teicher and associates reply. Am J Psychiatry *147*: 1692–1693

Teicher M H, Glod C, Cole J O (1990c) Dr Teicher and associates reply. Am J Psychiatry *148*: 1260–1262

Tollefson G D, Greist J H, Jefferson J W, Heiligenstein J H, Sayler M E, Tollefson S L, Koback K (1994) Is baseline agitation a relative contra-indication for a SSRI: a comparative trial of fluoxetine versus imipramine. J Clin Psychopharmacol *14*: 385–391

Van der Sande R, Van Rooijen L, Buskens E, Allart E, Hawton K, Van der Graaf Y, Van Engeland H (1997) Intensive in-patient and community intervention versus routine care after attempted suicide. Br J Psychiatry *171*: 35–41

Wheatley D, van Moffaert M, Timmerman L *et al.* (1998) Mirtazapine: efficiency and tolerability in comparison with fluoxetine in patients with major depression. J Clin Psychiatry (in press)

WHO (1994) International monitoring of adverse reactions to drugs. Adverse reaction terminology. WHO, Geneva

Wirshing W C, Van Putten T, Rosenberg J, Marder S, Ames D, Hicks-Gray T (1992) Fluoxetine, akathisia and suicidality: is there a causal connection? Arch Gen Psychiatry *49*: 580–581