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Death, dependence and deception

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Where other distinguished journals have balked, the *Journal of Psychopharmacology* has uniquely provided a forum for debate on the important issues of both theoretical and clinical importance linked to the use of psychotropic drugs, particularly the selective serotonin reuptake inhibitors (SSRIs) (Healy, 2003). The constructive review of these issues by David Nutt (2003) moves this debate onto a different plane. We will take the chance to comment on some of the points he raises under his original headings of 'Death' and 'Dependence', and under a further heading of 'Deception'.

Death

On the question of whether antidepressants, and in particular SSRIs, may cause problems for some individuals, we find ourselves in complete agreement with David Nutt's suggestion that doctors and patients should be warned about the possible risks of activation on these drugs. In the presence of proper warnings, we would agree with him that antidepressants could conceivably be used not just to improve quality of life for patients who are depressed, but also potentially to reduce national suicide rates. In the absence of warnings, there is now abundant evidence that many prescribers recommend a doubling of the dose of treatment when faced with patients who appear to be doing worse in the early stages of treatment.

Dr Nutt mentioned that national suicide rates have fallen in a number of countries in recent years, and that this may be linked to the use of SSRIs as opposed to either more hazardous agents or non-treatment. It is difficult to extrapolate from clinical trial data to national suicide rates, but it is perhaps worthy of note that, in the past year, the national rates for some of the countries invoked in this debate (i.e. USA, Finland and Holland) have all remained static or have risen against a background of steadily increasing antidepressant consumption [1]. [US data provide figures of 10.46/100 000 population for 1999, 10.43 for 2000 and 10.73 for 2001, with an uncorrected figure of 10.6 for 2002 (http://www.cdc.gov; injuries prevention site). These figures need to be set against a background of rapidly rising figures for antidepressant consumption. Dutch figures give 11.8/100 000 population for 1999, 11.6 for 2000, 11.0 for 2001 and 12.0 for 2002 (The Central Bureau for Statistics, 28/1/2004). For Finland, see Helsingin Sanomat, Suicides on the rise again (http://www.helsinki-hs.net/news.asp?id=200305191E3; accessed 19/05/2003)].

On the question of suicidal ideation and antidepressant use, David Nutt makes a number of important points. We would agree fully that it is difficult to extrapolate from suicidal ideation *per se* to suicidal acts or completed suicides. However, in this respect, treatment-induced suicidal ideation may be quite different to suicidal ideation in general in that, superficially at least, an abrupt and unexpected onset of suicidal ideation would appear to be potentially more malignant than a background or chronic state of suicidal ideation. For example, it is generally recognized that the risk of suicide associated with delusional beliefs is greatest in the period close to the onset or disappearance of those beliefs (Mayer-Gross *et al*., 1979).

Dr Nutt introduces a useful distinction between the energizing and activating effects of antidepressants that has not been widely considered in the current debate, and which would appear to merit further exploration. One method to separate out these effects is through healthy volunteer studies. Here, he contrasts the many studies undertaken by his group against others that have not revealed a problem and notes that, in a study of healthy volunteers by Healy (Year), those who became suicidal had previous exposure to reboxetine before becoming suicidal on sertraline. However, there are a number of other sertraline healthy volunteer studies with comparable results that did not involve previous exposure to other drugs, notably those conducted by Saletu *et al*. (1986) and Hindmarch and Coauthor/et al. (Year). Saletu *et al*. (1986) found a dose-dependent induction of agitation on sertraline in volunteers who had not been on previosu treatment and there is at least one unpublished phase one study involving sertraline, which led all volunteers taking sertraline to discontinue because of agitation (again, there was no previous exposure to other agents). The agitating effects of sertraline in this latter study appear to have been attributed to a dose-dependent effect by one outside commentator [C. Nemeroff, personal communication to D.H.]. It may be that differences observed by investigators in healthy volunteer studies relate to dose-dependent effects but, if so, this would concede

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causality. This important study, however, remains unpublished, and is a matter that will be dealt with further under the third heading.

Dependence

It is quite possible that all parties involved in the debate regarding SSRIs and dependence could agree with David Nutt in his summary of his confusion surrounding the word addiction. However, it is these very confusions that make it important for clinicians, opinion leaders and pharmaceutical companies to take account of the likely meaning that such words have for the public. In this regard, it is not reasonable to castigate Panorama, when WHO acknowledges the situation as problematic and cannot find a way to resolve the complexities.

Dr Nutt divides the problems previously associated with physical dependence into 'rebound' and 'discontinuation' syndromes. One problem with this formulation is that both the Committee on Safety of Medicines and CPMP have refused to accept the term 'discontinuation syndrome'. It alo appears that Glaxo SmithKline have stopped using the term discontinuation syndrome in favour of 'symptoms on stopping' (SoS) (http://www.paxilcr.com/Paxil_CR_Side_Effects.jsp).

The key issue here relates to how long any SoS are likely to last. The early work by the Bristol group isolated some of the key symptoms, helped put the syndrome on the map, and suggested that the problem might not be unduly severe (Coupland *et al*., 1996). At least one pharmaceutical company availed of the opportunity that this work threw up to gain a competitive advantage over other SSRIs and, in the process, suggested that withdrawal syndromes could be 'clinically relevant' (Dear Doctor letter from Eli Lilly 1997, Prozac helps avoid discontinuation syndrome. Available from D.H.).

Subsequently, it has become clear that, in addition to a number of the symptoms outlined in early reports of this syndrome, anxiety, depression and irritability are probably the commonest symptoms experienced by those withdrawing from treatment and, when this is taken into account, estimates of the frequency with which these problems occur rise to over 25% (Rosenbaum *et al*., 1998).

It is difficult to make judgements based simply on clinical impressions as to how problematic withdrawal syndromes of this kind can be. However, we have recently been working on a model that converts pills used per annum into patients (this model to convert drug usage into numbers of patients has been reviewed and validated by the MHRA. It is currently being developed for peer review). Using rates of paroxetine and fluoxetine usage provided by the Department of Health from 1991 through to the present, and data on likely lengths of treatment stemming from DSRU studies (Inman *et al*., 1996), this model suggest that there are at present 350 000 patients taking paroxetine in England for more than 1 year, and over 400 000 taking fluoxetine. These figures suggest that there may be over one million people taking SSRIs chronically (over 2% of the population).

Seen against a background of epidemiological work that consistently indicates that the mean length of an affective episode is 12–16 weeks (Spijker *et al*., 2002; Kessler *et al*., 2003), a figure of 2% of the population being treated for over 1 year, despite guidelines recommendations to treat for up to 6 months, suggests that a large number of people must receiving a treatment that they do not need. It is less clear whether this is caused by an inability to stop the drugs, or the failure by treating clinicians to realize that difficulties on withdrawal are withdrawal problems rather than new illness episodes.

What is more clear is that when these drugs were first marketed, for whatever reason, both patients and prescribers appear to have ended up with incorrect notions as to whether there were likely to be problems on withdrawal.

Deception

As David Nutt outlined, the regulators in Britain and other countries have recently recommended against the use of all SSRIs for minors, and have specifically indicated that the risk of suicidal acts on paroxetine in clinical trials is between 1.5 and 3.2-fold greater than the risk on placebo (Glaxo SmithKline, 2003). In the process, data that would otherwise be concealed have emerged into the public domain. Data in the public domain suggest that the risk of aggression on paroxetine is 10-fold greater than on placebo (Glaxo SmithKline, 2003). The risks of suicide and aggression are twofold as greater on venlafaxine compared to placebo (Kuslak, 2003). Comparable figures can be deduced from published articles on sertraline, or from documents in the public domain (Pfizer Expert Report, 1997).

By contrast, the published articles or abstracts on paroxetine, venlafaxine and sertraline universally report these drugs as being safe, well-tolerated and, except in the case of venlafaxine, effective (Mandoki *et al*., 1997; Alderman *et al*., 1998; March *et al*., 1998; Ambrosini *et al*., 1999; Keller *et al*., 2001; Carpenter *et al*., 2002; Geller *et al*., 2002; Wagner *et al*., 2002, 2003).

The repeated designations of these drugs as safe, effective and well-tolerated points to a major discrepancy between publications linked to pharmaceutical companies and the raw data from clinical trials on the sponsor's drug. Such a discrepancy, perhaps the biggest in medicine, will inevitably lead to differences of opinion among academics in their interpretation of the evidence.

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