

Prozac — is it worthy of the hype?

In the fourth article in a series on landmark drugs, John Donoghue takes a look at Prozac and the massive media attention it has received over the years. Has Prozac delivered what it promised?

Hindsight is a great thing; it always comes with 20:20 vision. A cliché perhaps, but often paraded as true, nonetheless. However, an event occurred 20 years ago, the outcomes of which, even with the benefit of hindsight, many find difficult to credit.

The year 1988 saw a number of momentous world events. The Soviet Union withdrew its forces from Afghanistan, Pan Am flight 103 crashed on Lockerbie, Benazir Bhutto became the first woman leader of an Islamic country, the Turin shroud was declared a fake, Roy Orbison died, the human genome project was started and Harry Enfield told us all about “Loadsamoney”. It was the first time we wore red noses to raise money for charity, Dustin Hoffman won an Oscar for his role in “Rain Man” and CDs outsold vinyl for the first time. NASA scientist James Hansen warned the US congress about the dangers of global warming and the greenhouse effect, George Bush senior told the American electorate to “read my lips” and, so quietly it went completely unnoticed by most people, a future icon was introduced to an unsuspecting world: Prozac.

Prozac (fluoxetine) was a member of a new class of antidepressants, the selective serotonin reuptake inhibitors, or SSRIs as they quickly became known. Its development came from a combination of serendipity and self-interest but for a long time its future was in doubt. Its discoverers, researchers working for Eli Lilly, were unconvinced that it would have any value as an antidepressant, and it languished for 16 years from its discovery in 1972 to its launch in 1988. It was not the first of the SSRIs, nor has it been the last, but, without any doubt, it has been the most successful, achieving an iconic status shared with few other medicines. How did this success happen? Was it a result of aggressive and perhaps cynical marketing? Was it because of a sea-change in societal attitudes that became more accepting of the medicalisation of emotional distress? Or did this new class of medicines really offer important clinical advantages to people with depression?

A well-oiled machine

Eli Lilly possessed a slick and competent marketing machine. From the outset, the advantages of Prozac over the market-leading tricyclic antidepressants (TCAs) — in the UK amitriptyline and, as it was then known, dothiepin — were emphasised. The problems associated with the TCAs, ie, cardiotoxicity, anticholinergic effects and daytime sedation



Garo/Phantize/Rex Features

were absent with Prozac. But by itself, this was not enough to explain its phenomenal growth. In the UK, just four years after its launch, a golden opportunity arose. There was to be a national “Defeat depression” campaign; Lilly would align itself and its marketing closely with it.¹ Part of the campaign was to stress the importance of the correct dosing of TCAs — a concern that had been debated by psychiatrists for some years.² With Prozac, of course, the daily dose of 20mg was the effective dose — no need for any messy titration. But still that was not enough. Then in the mid 1990s, two unconnected but highly influential pieces of research emerged. The first came from the National Poisons Unit, which created a fatal toxicity index for antidepressants.³ The most commonly prescribed TCAs were among the most toxic in overdose (an all too common occurrence in depression), while Prozac was among the least. The second was the finding of large epidemiological studies confirming beyond doubt that the vast majority of prescriptions written for TCAs in primary care were at doses that were really too low to be effective, while the SSRIs were almost always prescribed at an effective dose.⁴ The marketing of Prozac was quickly aligned with these discoveries. Although other researchers published meta-analyses showing that in clinical trials SSRIs were no better tolerated than TCAs, it was too late.^{5,6} The twin platforms of fatal toxicity and sub-optimal use had let the genie out of the bottle.

But it did not end there: Lilly sponsored further research to show that among the SSRIs, Prozac was the one that was used to best advantage.⁷ And when, some years later, it emerged that with some SSRIs, particularly paroxetine, unpleasant symptoms could emerge on stopping treatment,^{8,9} Prozac marketing took full advantage of this as well, in the knowledge that with its long half life Prozac was highly unlikely to cause such problems.

An icon in the making

The marketing of Prozac took place in a period of rapid societal change, particularly in the US. The economy was buoyant and the mood was optimistic; everybody, it seemed, had the right not to be unhappy. In particular, the growth of the cult of the celebrity provided a perfect vehicle for Prozac. The media rapidly endowed it with a personality, and it came to be the darling of talk shows, featuring on the covers of international magazines and inspiring a number of books including ‘Listening to Prozac’ and ‘Prozac Nation’.^{10,11} The BBC made it the subject of an *Everyman* programme called “Welcome to Happy Valley” that was set in Washington State, dubbed the “Prozac capital of the world”. It was the focus of the movie “Brain Candy” (where it was called Gleemonex, although everybody knew what it stood for). America was said to be going crazy for the happy pill and it was hailed as the “Elvis of pharmaceuticals”.¹² Talking about emotional

John Donoghue is a pharmaceutical consultant in mental health (e-mail john@johndonoghue.orangehome.co.uk)

distress became not just acceptable, but desirable, and Prozac was described as being as familiar as Kleenex and as socially unremarkable as mineral water. Opinions about Prozac quickly polarised. At one extreme psychiatrist Peter Breggin and the Prozac Survivors' Support Group deplored the type of "quick fix" solutions to society's personal, social and spiritual problems that Prozac seemed to offer. Occupying the centre ground was Peter Kramer who, in 'Listening to Prozac',¹⁰ took a serious look at the phenomenon that Prozac had become and, although he should not be considered an apologist for Prozac, did invite criticism when he defended what he called cosmetic pharmacology. At the other pole were many family physicians and psychiatrists trying to do their best to help their patients, many of whom were only too happy to appear on television shows to tell any who wanted to listen how Prozac had helped them. The possibility was raised that the benefits of Prozac were not limited to treating depression, but offered opportunities for pharmacological personality reconstruction — thus medicalising unhappiness. Naturally, the media, sensing a story that was in tune with the times and was set to run, were only too happy to follow and even to try and direct it. They gaily played off the therapeutic puritans, who judged it to be morally imperative to tough it out or call on a higher power when faced with emotional distress, against the enthusiasts, who saw nothing wrong in attempting to improve mood and perceptions with an antidepressant, even if it was just to help with the ups and downs of everyday life.

The reality

Did Prozac and the other SSRIs deliver the therapeutic revolution that they seemed to promise? As with all revolutions there were both positive and negative aspects. Although clinical trials suggested that they had efficacy similar to the older TCAs, SSRIs were less toxic in overdose and their wider use clearly improved the intensity with which antidepressant treatment could be delivered in primary care settings.¹³ Although this was not quite the heady stuff of revolution, years later it came to be reflected in advice from the National Institute for Health and Clinical Excellence (NICE) on the selection of an antidepressant,¹⁴ with a systematic review by NICE confirming what everybody already knew: that SSRIs were similarly efficacious

but better tolerated than TCAs.¹⁵ That is not to say that they are without important adverse effects. NICE considered the potential for problems with anxiety, agitation, akathisia, restlessness and thoughts of suicide with SSRI antidepressants to be so great that health professionals were advised to look for them proactively and specifically warn patients about them.¹⁴ Other problems include sexual dysfunction (which has been reported to occur in as many as 70 per cent of SSRI-treated patients),¹⁶ inhibition of hepatic cytochrome P450 metabolic enzymes leading to potentially important drug interactions and discontinuation syndromes, particularly with paroxetine.⁹

The emergence of discontinuation symptoms resurrected fears about dependence associated with antidepressants, first identified in the Market and Opinion Research International (MORI) poll conducted during the "Defeat depression" campaign,¹ later given credence in a BBC *Panorama* programme and likely to militate against treatment adherence in the long term.

Where SSRIs have not proven helpful is in treating disturbed sleep — an important symptom of depression, and its importance is often underestimated. Intractable sleep disturbance increases the risk of relapse, but SSRIs are associated with increased sleep disruption until after the underlying depression has improved. Clinicians may resort to using sedative TCAs or drugs like trazodone or mirtazepine, though this is often at the expense of sub-optimal doses or other adverse effects like weight gain.

The idea that Prozac and the other SSRI antidepressants augured a therapeutic revolution in the treatment of depression is open to debate. Improvements in the management of depression have evolved rather than appeared with dramatic suddenness. Antidepressants introduced since the SSRIs, like venlafaxine and mirtazepine, have shown few, if any, advantages over the SSRIs. A new gold standard antidepressant, that has better efficacy than currently available treatments, helps with sleep disturbances and reduces still further the burden of adverse effects including discontinuation symptoms remains elusive. Several compounds are in development that are not pharmacologically selective — like the SSRIs — but which are seeking to enhance the antidepressant effect by activity at multiple sites. The current advice from NICE is that when an antidepressant is prescribed in routine care,

SSRI antidepressants, particularly citalopram or fluoxetine should be considered because they are as effective as TCAs but less likely to be discontinued because of side effects.¹⁴ These are the twin standards by which any new antidepressant must be measured before being given the opportunity to launch the next therapeutic revolution.

References

1. Paykel ES, Priest RG. Recognition and management of depression in general practice: consensus statement. *BMJ* 1992;305:1198–202.
2. Kendrick T. Prescribing antidepressants in general practice. *BMJ* 1996;313:829–30.
3. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. *BMJ* 1995;310:221–4.
4. Donoghue JM, Tylee A. The treatment of depression: prescribing patterns of antidepressants in primary care in the United Kingdom. *British Journal of Psychiatry* 1996;168:164–8.
5. Anderson IM, Tomenson BM. Treatment discontinuation rates with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995;310:1433–8.
6. Hotopf M, Hardy R, Lewis G. Discontinuation rates of SSRIs and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. *British Journal of Psychiatry* 1997;170:120–7.
7. Donoghue JM. Selective serotonin reuptake inhibitor use in primary care: a five-year naturalistic study. *Clinical Drug Investigation* 1998;16:453–62.
8. Haddad P, Lejoyeux M, Young A. Antidepressant discontinuation reactions. *BMJ* 1998;316:1105–6.
9. Tonks A. Withdrawal from paroxetine can be severe, warns FDA. *BMJ* 2002;324: 260.
10. Kramer PD. *Listening to Prozac*. New York: Penguin Books, 1993.
11. Wurtzel E. *Prozac nation*. New York: Riverhead Books, 1995.
12. Elliott C. The Elvis of pharmaceuticals. *BMJ* 1996;313:950.
13. Dunn RL, Donoghue JM, Ozminkowski RJ, Stephenson D, Hylan TR. Longitudinal patterns of antidepressant prescribing in primary care in the United Kingdom: comparison with treatment guidelines. *Journal of Psychopharmacology* 1999;13:136–43.
14. National Institute for Health and Clinical Excellence. Depression (amended): managing depression in primary and secondary care. *Clinical Guideline 23 (amended)*. London: National Institute for Health and Clinical Excellence, April 2007. Available at: www.nice.org.uk (accessed 19 November 2007).
15. National Institute for Health and Clinical Excellence. Depression: managing depression in primary and secondary care. *Clinical Guideline 23; Full Guideline*. London: British Psychological Society and the Royal College of Psychiatrists, 2004. Available at: www.nice.org.uk (accessed 10 November 2007).
16. Kennedy SH, Eisfeld BS, Dickens SE, et al. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *Journal of Clinical Psychiatry* 2000;61:276–81.

The Royal Pharmaceutical Society's Panel of Fellows is empowered to confer fellowship on members of not less than 12 years' standing who have made an outstanding original contribution to the advancement of pharmaceutical knowledge or have attained distinction in the science, practice, profession or history of pharmacy.

A pharmacist wishing to nominate a colleague for fellowship needs the support of at least two other pharmacists. At least one of those making or supporting the nomination must be a fellow. The nominator should provide a detailed biographical profile of the nominee, clearly showing the contribution made to pharmacy through their career. The biographical details should also include information about involvement in civic affairs or other voluntary work on

behalf of the community (this assists the panel in putting into context the nominee's contribution to the profession).

Nominations and inquiries about the nomination procedure should be addressed to Roger Odd, Secretary of the Panel of Fellows, Royal Pharmaceutical Society, 1 Lambeth High Street, London SE1 7JN (tel: 020 7572 2203). There are no official nomination forms.

The panel meets each May and November. The closing date for nominations is 1 March (for May) or 1 September (for November). The panel's decisions are reported to the Council in June and December so that authority can be given for affixing the Society's official seal to the fellowship certificates. Although appointed by the Council, the panel does not include any Council member.