

## Editorial

## The 25th anniversary of the launch of Prozac gives pause for thought: where did we go wrong?

Edward Shorter

**Summary**

The creation, in DSM-III, of the category 'major depression' can be linked to the launch, and success, of Prozac. The consequences of creating this broad diagnostic category are of concern in relation to the treatment of individuals with a diverse variety of depressive disorders.

**Declaration of interest**

None.

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Prozac was launched in the USA in 1988 (and in the UK the following year). But the story begins with DSM-III<sup>1</sup> in 1980, which created the category 'major depression'. Major depression, a highly heterogeneous concept, included a wide variety of disorders, ranging from old-fashioned 'nerves', which included mild depression, through the traditional depressions of the pre-1980 period, including reactive depression and neurotic depression, through to frank melancholia, the prostrate patient sobbing and curled into a fetal ball. All this became major depression, and there were few agents to which some portion of this highly variegated patient population did not respond. Some responded to exercise therapy and *Ginkgo biloba*, some to electroconvulsive therapy (ECT).

**The launch of Prozac**

Major depression created a perfect portal through which agents could be driven without having to demonstrate specific efficacy in any particular type of depression. However low their absolute effectiveness in the real world, if they could stagger across the finish line in the major depression population, they would be licensed. This is what Lilly accomplished in 1988 with Prozac (fluoxetine). In six of the eight studies that Lilly submitted to the USA Food and Drug Administration (FDA), Prozac failed to convincingly beat placebo, and in four there was no difference.<sup>2</sup> Nonetheless, Prozac won rather reluctant acceptance from the authorities (in 1987) on the grounds that only two positive trials were necessary. (An English-second-language member of the advisory committee of the FDA said during a meeting on Prozac, 'So, suppose all eight people [trialists] publish their papers, that would end up like a disaster.'<sup>2</sup>)

What Lilly had created was essentially a revved-up antihistamine, tweaking the platform of diphenhydramine into a molecule that had a more specific effect on the reuptake of serotonin than on other neurotransmitters. It had something of an effect on anxiety and obsession–compulsion but would not have been considered an antidepressant had the company not chosen to market it as one. Why? One recalls that the anxiety market in the late 1980s was declining. The chief anxiolytic agents had been

the benzodiazepines, first marketed in 1960; a rather unfair miasma of addictiveness had come to hang about them, and, correspondingly, about the treatment of anxiety itself.

Depression, by contrast, was wide open. 'Major depression' was out there just for the plucking, and the truly effective antidepressants, of which there were several – including the monoamine oxidase inhibitor (MAOI) tranylcypromine and the tricyclic antidepressants – were unpopular either on the grounds that patients did not like them (dry mouth) or that clinicians had never really been exposed to these agents during training and were loathed to prescribe them. (Electroconvulsive therapy suffered the same disadvantage: if you did not learn about it as a registrar, you would not prescribe it as a consultant.)

Thus, when Lilly brought out Prozac, the company was essentially marketing two concepts: (a) depression, as a pure diagnostic entity: no more 'mixed depression–anxiety'; no more fussy distinctions between melancholic and non-melancholic depression; and (b) a plausible scientific story. Lilly's first advertisement trumpeted Prozac as 'the first highly specific highly potent blocker of serotonin uptake',<sup>3</sup> implicating a scientific mechanism. The message to the public and medical profession: we know this is potent stuff because we, unlike any other company, understand the science behind it. (The claim was wrong on historical grounds: US advertising copy for trazodone (Desyrel) in 1982 claimed that it 'selectively limits serotonin uptake in the brain'.<sup>4</sup> But the effect is a weak one and trazodone is not in fact a selective serotonin reuptake inhibitor (SSRI).)

The indication of depression and the mechanism of reuptake inhibition, linked together, were like a powerful locomotive, and pulled Prozac at high speed onto the market. A decade later, in 1996, Lilly claimed that since 1986 (the Belgian launch), Prozac had been prescribed for 'more than 21 million patients in 90 countries around the world'.<sup>5</sup> The uptake of Prozac became almost a cultural phenomenon, comparable with the fashion for high-protein and low-carbohydrate diets to lose weight: 'Washington City full of Prozac', headlined the *New York Times* in 1994.<sup>6</sup> City full of Prozac. Just imagine. I am not aware of comparable historical claims for any other pharmaceutical agent, penicillin included.

**Reasons for Prozac's success**

What is going on here? How do we account for this success? It was partially a result of relentless marketing, undertaken with an

intensity not hitherto seen in pharmaceuticals. By 1993, Lilly had 1600 sales representatives in the field in the USA, surpassed only by SmithKline Beecham's 1800 reps for Paxil – both trouncing Pfizer's mere 1250 for Zoloft.<sup>7</sup> The numbers are hallucinatory. By 2001, three of the top ten drugs in the USA were SSRIs (Zoloft at number 6, Paxil at number 7, Prozac at number 9).<sup>8</sup>

Another part of the story is the public's attachment to 'science' and its willingness to be seduced by products for which an evident scientific basis could be argued. The claim that the superiority of one's product rests on scientific doctrines about the inhibition of neurotransmitter uptake, condensed into the marvellous acronym 'SSRI', conferred an enormous marketplace advantage. And the claims reached an avid public: the number of references to 'neurotransmitters' in the *New York Times* rose from 18 in 1955–1960, to 67 in the 1980s, to 168 in 1991–2000.<sup>9</sup>

In retrospect, much of the science is trivial. We still have no idea how the chemistry of the brain produces affective disorders. Ross Baldessarini, a senior research psychiatrist at the McLean Hospital in Massachusetts, dismissed the whole argument that deficiencies in neurotransmitters resulted in clinical illness: 'We have [pursued fads] in much of biological psychiatry, including grossly overvaluing our partial understanding of the pharmacodynamics of some drugs as a putative route to clarifying the pathophysiology of psychiatric illnesses'.<sup>10</sup> He scorned theories linking one neurotransmitter to one disease, such as serotonin to depression. These emphases, he said, had kept the field stuck on the study of 'old mechanisms and old theories'.<sup>10</sup>

The story is certainly more powerful than a handful of biogenic amine neurotransmitters. But it captivated the attention of the public, making 'Prozac era' a watchword for our fin de siècle. And then the air went out of the tyre. In 2001, the Prozac patent expired. Lilly stopped promoting the drug, and the byword for an era gradually shrank from medical view. It was time to look around for the new Prozac. But there was, and is at this writing, nothing on the horizon.

### Consequences for the treatment of depression

In retrospect, what have been the results of the Prozac vogue for medical practice and drug development? They are, on the whole, quite negative.

First, virtually all previous psychoactive mood agents – I loathe the term 'antidepressants' – have been forgotten. The SSRIs had approximately the same impact on psychopharmacology as psychoanalysis had on previous learning in psychiatry: the slate was wiped clean. No one today can even remember the names of the agents in the 1980s that had considerable effectiveness: maprotiline, nomifensine, the whole row of benzodiazepines, the MAOIs such as the abovementioned tranylcypromine: all forgotten. I will be quite surprised (dumbfounded) if any practitioner younger than 50 writes to me and says, 'Oh, Edward, you're very much wrong about meprobamate' (or whatever the cherished historic agent is). The older and often quite effective

agents really have been wiped from mind. And although the tricyclic antidepressants remain in the pharmacopoeia for practitioners whose first instinct in the treatment of melancholia is not ECT, they are not widely prescribed.

Second, 'major depression' has become cast in concrete as a diagnosis, and has been carried over into DSM-5.<sup>11</sup> This is a nosological disaster because the diagnosis, as noted, is quite heterogeneous. Yet the SSRIs fit major depression hand-in-glove, and many practitioners do not for a moment doubt its existence – nor are they widely familiar with melancholia – because 'major depressive disorder' has been drummed into their heads for the past 30 years. Yet melancholic and non-melancholic depression are quite separate illnesses,<sup>12</sup> and lumping them together means that potentially suicidal patients are inappropriately treated with fluoxetine.

Third, drug discovery in the mood area has virtually come to an end. The companies all wish to capture the 'next Prozac,' and concentrate their discovery efforts on 'antidepressants'. It is no surprise that they have, in 30 years of striving, come up with little because major depression does not exist as a diagnostic entity, and drug development programmes aimed at this inconstant target will inevitably fail.

The whole Prozac story is a cautionary tale for medicine and the pharmaceutical industry: in treatment and diagnosis, older is very often better.

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First received 29 Sep 2013, accepted 6 Mar 2014

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