

Eternal sunshine

It's sold as happiness in a blister pack - a cure-all that has changed the way we think about wellbeing. As Prozac reaches its 20th birthday, Anna Moore presents 20 things you need to know about the most widely used antidepressant in the world

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1: Depression has deepened

In 1971, when LY110141 - the compound that became Prozac - was developed, depression was rarely discussed and antidepressants largely restricted to the psychiatric unit. People went to their GPs with 'anxiety' and 'nerves'. Tranquillisers such as Valium were a likely response.

Eli Lilly, the company behind Prozac, originally saw an entirely different future for its new drug. It was first tested as a treatment for high blood pressure, which worked in some animals but not in humans. Plan B was as an anti-obesity agent, but this didn't hold up either. When tested on psychotic patients and those hospitalised with depression, LY110141 - by now named Fluoxetine - had no obvious benefit, with a number of patients getting worse. Finally, Eli Lilly tested it on mild depressives. Five recruits tried it; all five cheered up. By 1999, it was providing Eli Lilly with more than 25 per cent of its \$10bn revenue.

Fluoxetine was handed to Interbrand, the world's leading branding company (Sony, Microsoft, Nikon, Nintendo) for an identity. The name Prozac was picked for its zap: it sounded positive, professional, quick, proey, zacky. It was marketed in an easy-to-prescribe 'one pill, one dose for all' formula and came when the medical profession and media were awash with horror stories about Valium addiction.

Prozac hit a society that was in the mood for it. National campaigns (supported by Eli Lilly) alerted GPs and the public to the dangers of depression. Eli Lilly funded 8m brochures (Depression: What you need to know) and 200,000 posters. Previous antidepressants were highly toxic, lethal if overdosed on and had other nasty side-effects. Prozac was pushed as entirely safe, to be doled out by anyone. It was the wonder drug, the easy answer, an instant up, neurological eldorado. When launch day dawned, patients were already asking for it by name.

Twenty years on, Prozac remains the most widely used antidepressant in history, prescribed to 54m people worldwide, and many feel they owe their lives to it. It is prescribed for depression, obsessive compulsive disorder, panic disorder, eating disorders and premenstrual dysphoric disorder (formerly known as PMT). In the UK, between 1991 and 2001, antidepressant prescriptions rose from 9m to 24m a year.

Strangely, depression has reached epidemic levels. Money and success is no defence: writers, royalty, rock stars, supermodels, actors, middle managers have all had it. Studies suggest that in America, depression more than doubled between 1991 and 2001. In the UK, an estimated one in

six people will experience it - and it costs more than £9bn annually in treatment, benefits and lost revenue. Meanwhile, according to the World Health Organisation, depression is set to become second only to heart disease as the world's leading disability by 2020.

2: Bio-babble has replaced psychobabble

Serotonin was not well known 20 years ago. Now, if you ask the person sitting beside you what it is, he or she may tell you it is linked to happiness, that levels get low in depressed people ... that Prozac tops them up ... so does chocolate ... or aerobics ... maybe yoga ...

Except it isn't strictly true. Or has been repeatedly challenged. And is yet to be proven. According to David Healy, professor of psychiatry at Cardiff University and author of *Let Them Eat Prozac*, it's pure 'bio-babble' which has replaced the psychobabble of the Sixties and Seventies. Healy spent a decade studying the neurotransmitter serotonin in depressed people and found little evidence to support the theory of 'chemical imbalance'.

'The idea was forwarded in the Sixties - and the man behind it, Dr George Ashcroft, later took it back,' says Healy. 'Through the Seventies and Eighties, it was seen as a simplistic idea; now it's seen as very convenient - it sounds so neat. There's something in you that's low that needs to be put right. It makes you happier to take a drug.' (Witness Brooke Shields, who described it as 'comforting' to discover her depression was 'directly tied to a biochemical shift'. Or the writer Lauren Slater in *Prozac Diaries* describing Prozac as 'a drug with the precision of a scud missile, launched miles from its target only to land, with a proud flare, right on the enemy's roof'.)

Prozac is a Selective Serotonin Reuptake Inhibitor (SSRI). Previous tricyclic antidepressants (TCAs) worked on three neurotransmitters associated with mood (serotonin, dopamine and noradrenaline) whereas Prozac just concentrates on one: serotonin.

'The idea that it's been a major step forward for Prozac to select serotonin only is just hypothesis,' says Malcolm Lader, professor of clinical psychopharmacology at the Institute of Psychiatry. 'There's no science behind it.'

The theory that emotions are governed by serotonin levels is highly simplistic and works just as well the other way around (ie, our emotions, our stress levels alter our brain chemistry, so it's at least a two-way street). Other important factors that contribute to depression include life experience, family history, hormones and diet. However, the oft-repeated 'chemical imbalance' theory (the fault is not in ourselves, but in our precious bodily fluids) is promoted on depression websites owned by drug companies and in advertising.

And just like scuds, Prozac turned out to be less precise than originally supposed. Experiences with it range from miraculous to mediocre. The writer Zoe Heller found that within weeks of taking it, she stopped crying and could get out of bed. Others describe it as a detached benevolence, or a comforting numbness. It makes some people feel anxious, agitated and unable to sleep. There are those who stop taking it, as they feel no effect at all.

Interestingly, reports gained through the Freedom of Information act revealed that in half the 47 trials used to approve the six leading antidepressants, the drugs failed to outperform the sugar pills. When they did, it was by only two points on a 52-point depression rating. Frosties, anyone?

3: You never too young

Enter liquid Prozac in peppermint flavour. In the US, a survey of drug companies found that between 1995 and 1999, use of Prozac-like drugs for children aged seven to 12 increased by 151

per cent, and in those aged under six by 580 per cent. In 2004, children aged five and under were America's fastest-growing segment of the non-adult population using antidepressants. 'Selective mutism' (fear of speaking in social situations) is one affliction common in preschoolers and has been treated with Prozac.

In the UK, too, the trend has been upwards. Between 1992 and 2001, prescriptions of SSRIs for under-18s increased tenfold - despite the fact that none has a licence for use in children. In 2003, the NHS warned against all SSRIs in under-18s except Prozac, after studies showed they rarely performed better than a placebo, and came with disturbing side-effects.

In America, the SSRIs, including Prozac, now carry a 'black box' warning that the drugs could increase suicidal behaviour in children. It's thought that prescriptions are falling in both countries as a result.

4: Animals are in on it too

Romain Pizzi, specialist in zoo and wildlife medicine for the Royal College of Veterinary Surgeons (RCVS), remembers prescribing Prozac to Mercedes, Edinburgh Zoo's polar bear.

'We can't say it's "depression" [the bear was suffering] but it's abnormal behaviour, a coping mechanism for animals held out of their natural habitat,' says Pizzi. 'Polar bears wake from hibernation and travel long distances in search of food - their instinct is to roam. Every spring, Mercedes would wake up ready for a massive migration and she'd start swimming and pacing a particular route, wearing her fur and skin down as she rubbed it in the same place. Large cats do the same, pacing, shaking their heads. Antidepressants dampen down some of the behaviour and, hopefully, reduce the stress.'

Pet parrots are also on the receiving end of antidepressants because they are highly intelligent birds that self-mutilate if bored, while cats and dogs may suffer from stress or separation anxieties. 'A dog can't sit on the sofa and discuss his worries, but he can howl the house down or chase his tail or chew everything to pieces,' says Mark Johnston, an RCVS specialist in small animals. 'Urinary marking is common in cats - it could be because he's being beaten up by other cats or another cat is coming in through the cat-flap.'

If training and behaviour modification are unsuccessful, about one in 10 animal patients will be given antidepressants. Reconcile is a newly launched beef-flavoured version of Prozac aimed at dogs. 'Drugs may sound drastic - but it could literally save their lives,' says Johnston. 'If you've got a dog that's persistently aggressive, you won't put up with it for long. The last option is euthanasia.'

5: Pain is the new pleasure

Prozac's high celebrity uptake helped make SSRIs the It-drug of the Nineties - the pharmaceutical Fendi bag. Where once celebrities sought to hide their depression - Marilyn Monroe, Audrey Hepburn, Vivien Leigh - the Prozac era has helped wipe away the stigma. Depression is part of the job description - celebrities are expected to suffer somehow, then preferably write about it in an autobiography (Ulrika Jonsson, Kerry Katona, Gazza) or talk about it (Winona Ryder, Dame Kelly Holmes, Melinda Messenger, Johnny Depp, Gail Porter, most comedians and half the cast of EastEnders) or be treated in Arizona clinics for addiction to antidepressants (Robbie Williams). Most usefully, their empty Prozac prescription bottles can be collected as pop art (Debbie Harry).

Prozac has also featured in some tragic celebrity headlines. Michael Hutchence was found to have taken the drug when he committed suicide. Diego Cogoloto murdered designer Ossie Clark

while psychotic on a mix of Prozac and amphetamines. Anna Nicole Smith died after what is thought to be an accidental overdose of prescription drugs - including Prozac. Five months earlier her son Daniel had died after mixing two SSRI antidepressants with methadone. Her dog, Sugarpie, was also on Prozac.

6: Prozactly, prozacted, prozactive, prozaction

Prozac is now in the dictionary, no more a slavish noun but a fully fledged adjective with rights of its own. According to the Cambridge Advanced Learner's Dictionary, someone lively and excited may safely be described as 'on Prozac'.

7: Booked on Prozac

Elizabeth Wurtzel's *Prozac Nation* placed the drug firmly on the literary map in 1994. At that point, Wurtzel was 26 and had everything her generation was supposed to want (long legs, long hair, rich friends, glib friends, false friends, smart remarks and a loft apartment in Greenwich Village), but she'd suffered depression for as long as she could remember (she first attempted suicide at summer camp, aged 12).

Her memoir starts with her parents' unhappy marriage and leads to countless breakdowns, hit-and-miss lithium prescriptions and hopeless love affairs. At the same time, though, Wurtzel gets into Harvard, wins a Rolling Stone college journalism award, works as an arts reporter, drives around England in a BMW and lives an impossibly cool rock'n'roll life of the sort only hallucinogens can provide.

The story ends on a high note with Wurtzel given a diagnosis of 'atypical depression' treatable with a new drug called Prozac. In the final pages, she feels safe in her skin, looking forward to each day - 'the black wave' has gone.

The New York Times dubbed Wurtzel 'Sylvia Plath with the ego of Madonna', while NME described the book as having 'the same relevance and resonance as *On The Road*, *Catch-22* and *Generation X*'. A massive hit, it brought home the latest dead-end whinge of youth culture and showed that being young, cool and gifted in the Nineties could still leave you cold; but worry not, there was now an answer - in green and cream capsule form.

Unfortunately, the story was hard to put down. Seven years later, Wurtzel was still taking Prozac but also addicted to Ritalin, pornography and tweezing her leg hairs. Now she wrote about them in a less gripping, less successful *More, Now, Again*. By the time the film of *Prozac Nation* was made, starring Christina Ricci as Wurtzel and Jessica Lange as her mother, America's love affair with Wurtzel was over and it went straight to DVD. She is now a student at Yale Law School.

More memoirs followed, including Lauren Slater's *Prozac Diary* (1998), which starts when she takes the drug and is finally freed from her OCD, which had resulted in suicide attempts, self-mutilation and five hospitalisations. After a decade on Prozac, she had a doctorate from Harvard, and was a writer, teacher and a wife.

A more recent addition was Brooke Shields's *Down Came the Rain*, an account of her struggle with postnatal depression, in which she was saved not by Prozac, but Seroxat, another SSRI which followed like a pilot fish in Prozac's unsleeping wake.

8: Tom Cruise vs Brooke Shields

In May 2005, Tom Cruise was promoting *War of the Worlds* and Shields was promoting *Down Came the Rain*. Scientologists are vehemently opposed to all forms of psychiatry. (According to L Ron Hubbard, psychiatrists are corrupt, barbaric and also members of a worldwide conspiracy bent on creating a government on behalf of Soviet Russia.) On NBC's *Today* show, Cruise took this theory a stage further and launched a personal attack on Brooke Shields, calling her 'irresponsible' for praising an antidepressant when vitamins and exercise would have cured her.

Papers and pundits debated before the anxious eyes of the world, polls polled ('Is Scientology killing Cruise's career?'; 'Should Cruise and Shields kiss and make up?'), Brooke Shields suggested Cruise stick to saving the world from aliens and let women with postnatal depression decide what treatment options are best for them. Watching at home was Paula Fortunato, wife of Sumner Redstone, chairman of Viacom (the enormous media company behind Paramount). She told her husband that Cruise's rant had turned female fans against him. Three months later, Cruise was fired after 14 years with the studio. 'Paula, like women everywhere, had come to hate him,' Redstone told *Vanity Fair*. 'The truth of the matter is I did listen to her. His behaviour was entirely unacceptable to Paula and to the rest of the world. He just didn't turn one woman off. He turned off all women, and a lot of men.'

9 Vanilla Ice is 'crazy like Prozac'

Vanilla Ice's 'Prozac' track featured in his strange 1998 comeback album *Hard to Swallow*, where he ditched his rap-for-teeny-boppers persona and came over all tattooed, pierced and head banging. There was a slight confusion over the lyrics ('We gets crazy like Prozac/ Hype enough to start a party and illy have a heart attack'), which seemed to be referring to a strong stimulant rather than a drug widely thought to be calming. It was suggested that Vanilla Ice - who has been treated for both depression and attention deficit disorder - got his prescriptions muddled.

One interviewer tried to clarify things with the singer. 'It confused me a little because "Crazy like Ritalin" is closer to what you guys do. You know, jumping around like you're hopped up on stimulants.' 'Yeah, that would work too,' agreed Vanilla Ice. The interviewer persisted: 'To me, Prozac would mellow you out, and you're certainly not mellow on this record.' Vanilla Ice replied, 'That's what Prozac does for you, you get crazy and you need Prozac. Crazy, like people on Prozac.' So that clears that up.

10: The ills are alive...

Prozac musical influences are also hinted at by Prozac Ruin (thought to be the best punk-rock band in Llanelli) and *Housewives on Prozac* (rock'n'roll mothers whose opuses include advice on fine dining: 'Eat Your Own Damn Spaghetti' and the slightly antisocial composition 'I Only Wanna Pee Alone'). Prozac songs are in strong supply: 'Prozac Smile' (The Dead Stars on Holiday), 'Daddy's on Prozac' (Joseph Arthur); 'All My Friends Are on Prozac' (Suffering and the Hideous Thieves) and 'Prozac vs Heroin' (The Brian Jonestown Massacre). Those of us with philosophical inclinations can reflect on the brevity of human existence with 'That Prozac Moment' (Mr T Experience).

11: The Prozac diet plan

Prozac has long been rumoured to help weight loss. Louise, 44, from Kent, was prescribed it for depression, but stayed on it longer than was strictly necessary when she found it suppressed her appetite. 'It was a very mild cocaine sort of feeling, an amphetamine speedy thing,' she says. 'I didn't get hungry and I was always doing stuff. I lost nearly a stone. My sister bought some online when she saw what it did to me.'

Brazilian Diet Pills, also widely available on the internet, contain fluoxetine, Prozac's active ingredient. In America, some doctors now prescribe Prozac to treat obesity - though it hasn't been approved for this purpose. The weight-loss company Nutrisystem also launched a diet programme, 'Phen-Pro' - a combination of Phentermine and Prozac - despite Eli Lilly's strong reservations.

In fact, trials have suggested that Prozac can result in an average, short-term weight loss of up to 7lb 4oz in obese patients. However, it has also been associated with weight gain after the initial loss of appetite wears off. (Louise is now the weight she was before taking them.) Weight gain on SSRIs is a popular topic in depression chatrooms.

12: Less sex

Though it can take 10 years for a drug to win its licence, the actual controlled, scientific studies used in evidence often last just four to six weeks. It's not surprising, then, that the existence or extent of most side-effects surface only after drugs have been taken up and tested in their millions by the general public.

Sexual dysfunction has turned out to be one of Prozac's hidden extras. Sarah, a 36-year-old stylist from London, who takes Prozac for panic attacks, has had a fairly typical experience. 'It has cured me and calmed me, but I haven't had an orgasm since the day I started,' she says. 'I still want to cuddle, but beyond that, I feel no physical arousal at all. Nothing. It's a trade-off. My partner can't decide which me he prefers. The neurotic, weeping basketcase who still enjoyed sex a few times a week or the calm and collected one that's completely frigid.'

The implications go beyond mere sex. According to Helen Fisher, anthropologist and author of *Why We Love: The Nature and Chemistry of Romantic Love*, SSRIs could seriously impede our ability to fall and stay in love. The bliss we feel when we're loved up - that elation, exhilaration and slight insanity - are the result of high levels of dopamine. SSRIs increase serotonin and curb dopamine. The result is that anti-love feeling, a contented, non-discriminatory 'well, whatever'.

Though initial tests put sexual dysfunction as present in fewer than 30 per cent of cases, the figure is now generally accepted to be more than 60 per cent, and a recent study put it at 98 per cent. With 54m people taking Prozac worldwide, that's a lot of sexual dysfunction. Symptoms include decreased or absent libido, delayed or absent orgasm, impotence or reduced semen volume in men and reduced vaginal lubrication in women.

13: More sex

On the upside, Prozac is now offered to men suffering from premature ejaculation.

14: Lives lost

Prozac has been persistently dogged by claims that it can trigger suicide - not just in depressives but also in healthy volunteers. Some SSRI users have reported agitation and an inability to keep still, a preoccupation with violent, self-destructive fantasies and a feeling that 'death would be welcome'. In Germany, Prozac was initially refused a licence after trials resulted in 16 attempted suicides, two of which were successful.

The SSRIs have made hundreds of court appearances. The first big case was in 1989, when Joseph Wesbecker walked through the Standard Gravure printing plant in Louisville, Kentucky with an AK47, killing eight employees, then himself. Wesbecker had been on the newly licensed

Prozac less than a month and had become increasingly agitated. The families of those killed sued Eli Lilly but agreed to a secret settlement.

More followed. After six days on Prozac, Patricia Williamson, 60, killed herself in her bath in Texas while her husband ate breakfast downstairs. Eli Lilly settled out of court. Don Schell had been on Seroxat (marketed as Paxil in America) for 48 hours when he shot his wife, his daughter, his nine-month-old granddaughter and himself at his home in Wyoming. Schell's son-in-law was awarded \$8m by manufacturers SmithKline.

In the UK, Reginald Payne, a retired teacher from Cornwall, suffocated his wife then he jumped off a cliff after 11 days on Prozac. His sons issued court proceedings against Eli Lilly. In *Losing a Child*, Linda Hurcombe describes the impact of her 19-year-old daughter Caitlin's suicide. Caitlin, from rural Shropshire, had asked her GP for Prozac, as she was feeling down; she had also heard it could help her lose weight. She had marked the subsequent days in her diary 'PZ Days'.

David Healy, who has testified as an expert witness against both Eli Lilly and SmithKline, estimates SSRIs can produce suicidal thoughts in one in 500 users.

15: Lives saved

According to most psychiatrists, the risk of not taking an antidepressant when suffering depression far outweighs any risks of taking them. For many users, the drugs can restore, even save, lives. Though depression appears to be on the increase, in this Prozac-enriched era the UK suicide rate - 8.5 deaths per 100,000 - is actually at its lowest level since records began.

Carmine Pariante, consultant psychiatrist at the Institute of Psychiatry, is sceptical of the claim that SSRIs carry a special suicide trigger. 'I remember having to be very vigilant in the first weeks of prescribing the old antidepressants, simply because before taking them, patients could be too low to commit suicide. They were then given a lift and possibly had the energy to put a plan into action.' The Institute of Psychiatry's Malcolm Lader agrees it is hard to prove, calling it 'a small signal against a very noisy background'.

Interestingly, there is also evidence that SSRIs lower non-suicide death rates in depressed patients. A study from Finland published in the *British Medical Journal* found antidepressants could reduce incidents of strokes and heart attacks.

16: Brushes with Prozac

The artist Stella Vine (right) named her 2004 exhibition, which featured such troubled subjects as Sylvia Plath and Courtney Love, after the drug. Vine - the former stripper now famous for her vivid, haunted portraits of Princess Diana, Kate Moss and the heroin victim Rachel Whitear - has herself yo-yoed on Prozac, finding it has both enabled her to function but blunted her painting.

'I remember when I was working as a nightclub hostess, one of the girls showed me her writing and it was really incredible. I asked why she had stopped and she said she started taking Prozac and couldn't write any more,' says Vine. 'I thought I'd never make that trade-off.'

In 2001, though, Vine did ask her GP for antidepressants. 'I've always been a highs-and-lows person, but this time, I was very, very depressed, just about doing the basics, the whole world collapsing, and when I started on Prozac, there was an incredible rush,' she recalls. 'I ate less, had more energy, I was speeding around the park with my dog, ecstatic to talk to the other dog walkers. It breaks the cycle of sitting on the sofa thinking about suicide, but in a way, it's a waste of time. Nothing is being sorted out and healed.'

Vine describes herself on Prozac as a 'la-di-da, hazy version'. 'I can paint the outline of a person, but I can't engage with any emotion in it,' she says. 'The really good work takes place when I'm not on Prozac. It's hard to describe, but it's more vivid and intense, a heightened awareness. I may have finished several undercoats and I get this great moment of absolute clarity. Suddenly I know what will make the whole thing work. That never happens on Prozac.'

Prozac's effect on creativity has been much debated - usually with the starter question 'What if Van Gogh had taken Prozac?' Perhaps he'd have given up art and become a life coach. Another possibility is that we'd now have more of his paintings.

17: Dilute to taste

In 2004, Prozac was discovered in our drinking water. The Environment Agency said the drug was building up in British rivers and ground-water supplies, probably via the sewage system. Some used it as evidence that Prozac was overprescribed. The Lib Dems called it 'a case of hidden mass medication upon the unsuspecting public'. The government's Drinking Water Inspectorate said the quantities were too diluted to have an effect (and poured themselves yet another glass, laughing maniacally through rolling eyeballs).

18: Prozac by post

Chicago artist Michael Hernandez de Luna created the fake Prozac stamp and successfully mailed it through the US postal system. Other de Luna stamps include an obese fast-food-fed Barbie doll and Monica Lewinsky's stained blue dress.

19: Enter Viagra

Pre-Prozac, drugs had names that were scientific and which referred to their compound. Prozac's branding and direct-to-consumer advertising, which has ultimately blurred 'ordinary life' with 'treatable illness', proved a valuable lesson in drug pushing. Enter Viagra, part medical treatment for sexual dysfunction, part lifestyle drug for sexual enhancement. Within two weeks of Viagra going on sale in the US, doctors were writing 40,000 prescriptions a day.

20 Goodbye Prozac, hello Cymbalta

All good things come to an end, though, and in 2001, Prozac lost its patent. Eli Lilly lost \$35m of its market value in one day - and 90 per cent of its Prozac prescriptions in a single year. Eli Lilly has now come back with Cymbalta, which it hopes will be the next Prozac. This was approved by America's Food & Drug Administration despite another very shaky start. Traci Johnson, a healthy 19-year-old college student, hung herself in the Eli Lilly laboratory while testing the drug at high doses, in return for \$150 a day. Cymbalta is a painkiller and antidepressant combined because, according to its logo, 'Depression Hurts'. Read all about it, carry out a self-assessment checklist and watch some inspiring real-life stories on www.cymbalta.com

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