50 years of SSRIs: weighing benefits and harms

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More than 50 years have passed since the discovery of fluoxetine, better known by its trade name Prozac. Together with the development of several other compounds, collectively known as selective serotonin reuptake inhibitors (SSRIs), fluoxetine transformed the treatment of depression and associated psychiatric conditions. SSRIs were better tolerated compared with older tricyclic antidepressants and a week's supply was not lethal in overdose. An estimated 332 million cases of major depressive disorder occurred in 2021. For many, SSRIs have been profoundly helpful in managing their health and continue to have an important place in care.

However, use of SSRIs has not been far from controversy and criticism. In 2004, the FDA issued a black box warning about a possible increased risk of suicidality in young adults taking an SSRI. It is now widely accepted that SSRIs can cause a protracted withdrawal syndrome, necessitating a gradual tapering when they are stopped. *The Lancet* understands that reports of serious adverse effects—specifically suicidality—are prompting renewed scrutiny of prescription guidelines and information for patients by the UK's Medicines and Healthcare products Regulatory Agency.

In her book *Chemically Imbalanced*, Joanna Moncrieff, Professor of Critical and Social Psychiatry at University College London, synthesises three key questions around the use of SSRIs. First, on effectiveness, Moncrieff references a 2002 meta-analysis, which concluded that compared with placebo their effects were clinically negligible. However, other studies have shown effectiveness, including a 2018 meta-analysis in *The Lancet*, which concluded that all antidepressants are more efficacious than placebo in adults with a diagnosis of major depressive disorder, with odds ratios ranging between 2·23 and 1·37.

Second, Moncrieff reviews the so-called serotonin hypothesis of depression. In 1975, Wong and colleagues reported that fluoxetine increased levels of serotonin in rat brains by blocking reuptake in the synapse. However, Moncrieff argues, indubitable evidence for the idea that low concentrations or reduced activity of serotonin in the brain is the problem remains elusive. Some psychiatrists have argued that delineating a clear mechanism of action is unimportant as long as the treatment is effective. Exploration of the pathophysiology of depression, however, will continue to generate lively scientific exchanges.

Third, Moncrieff comments on the "creeping medicalisation of a widening array of life problems". Certainly, there has been a growing tendency to medicalise misery or unhappiness, along with other aspects of the human condition, including worry, bad behaviour, and grief. A longitudinal study in New Zealand reported that 35% of people aged 11–15 years met the criteria for a mental disorder, rising to 44% at age 45 years; does this finding represent a true escalation in mental ill health, or is it a reflection of changing criteria of what qualifies as disease?

Additionally, the need for a quick fix is undoubtedly contributing to over-prescription and inappropriate use of medications. The latest NICE guidelines recommend that antidepressants should not be routinely offered as a first-line treatment for less severe depression, unless that is a person's preference—guided self-help should be the first treatment option. First-line treatments for more severe depression should be individual cognitive therapy combined with an antidepressant. However, provision of and access to non-pharmaceutical psychiatric services is patchy for many people and non-existent for others, funding is lacking, and many general practitioners are pressed for time and short on options. A pill, the reasoning goes, might be better than nothing. But the result is that for too many patients antidepressants are used readily, while there is little attempt to examine and address underlying psychosocial stressors. An analysis in *The Lancet Psychiatry* estimates that just 9·1% of women and 7·2% of men worldwide with a diagnosis of major depressive disorder receive minimally adequate treatment (which they define as either pharmacotherapy or psychotherapy). The result is a huge unmet medical need.

These arguments concerning SSRIs are riddled with controversy and many disagree with all or part of these ideas. Certainly, patients should not stop taking SSRIs nor physicians cease prescribing them. But 50 years on from landmark developments in drug treatment that were the cause of so much hope, we remain a long way from providing the level of care that so many people need, and this need continues to demand the attention of the scientific and medical communities. ■ *The Lancet*

For more on the **global burden of depression** see **Articles** *Lancet* 2024; **403:** 2133–61

For the **2002 study that found the effects of antidepressants to be negligible compared with placebo** see *Prev Treat* 2002; **5:** 23

For the **2018 *Lancet* meta analysis** see **Articles** *Lancet* 2018; **391:** 1357–66.

For more on the **serotonin hypothesis of depression** see *J Pharmacol Exp Ther* 1975; **193:** 804-11

For the **longitudinal study of mental health in New Zealand** see *JAMA Netw Open* 2020; **3:** e203221

For the **NICE guidelines for management of depression** see https://www.nice.org.uk/guidance/ng222