The Origins and Actions of Selective Serotonin Reuptake Inhibitors

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This study is an official narrative about antidepressants pitching them as successfully correcting a brain defect. This narrative, promoted by pharmaceutical company marketing departments, is at odds with the history of these medicines. The second-generation selective serotonin reuptake-inhibiting antidepressants were developed as a therapeutic principle acting on normal serotonin systems that might assist recovery in some but would not suit all people. The regulatory process through which medicines are licensed focuses on approving disease indications rather than treatment effects on function. The randomized controlled trials required for licensing purposes obscure what different kinds of antidepressants, acting on different systems and producing different effects accordingly, in fact, do. Obscuring these effects makes treatment more dangerous than it needs to be. The history of the selective serotonin reuptake-inhibiting antidepressants illustrates this as well, if not better than any other group of medicines, and in so doing holds lessons for clinical practice beyond mental health.

Keywords: antidepressants; mental health; adverse effects of psychiatric drugs; ethical psychiatry; critical psychiatry/psychology

Based on the early use of drugs to treat nervous problems, there was an expectation that novel psychotropic drugs would be nonspecific stimulants or sedatives, strengthening or calming nervous systems (Atigari & Healy, 2013). Rather than being specific to disorders, individual patients were viewed as likely to suit a stimulant or a sedative. Chlorpromazine, the first modern psychopharmaceutical, viewed through this lens, was initially called a tranquilizer or, alternately, a neuroleptic that was not specific to a particular condition. Its European trade name, Largactil, drew attention to its large range of actions.

Chlorpromazine was later redesigned as an antipsychotic, an apparently more specific term. The switch from a nonspecific tranquilizer to a specific antipsychotic designation was linked to the emergence of a group of drugs specifically called antidepressants from the start. In addition, changes to the Food and Drugs Act in 1962 tied the licensing of medicines to specific indications.

This article lays out a narrative about antidepressants as magic bullets that correct a brain lesion, which has been close to the standard view of these medicines for over half a century (Healy, 1997). This is followed by an account of the development of selective serotonin reuptake inhibiting agents that is at odds with the standard narrative, after

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which the implications of both the unofficial view and the mismatch between official and unofficial views are laid out.

ANTIDEPRESSANTS: THE OFFICIAL NARRATIVE

The idea that a medicine could be specifically antidepressant rather than nonspecifically stimulant or sedative emerged in the late 1950s with demonstrations that the tricyclic molecules imipramine and amitriptyline, and monoamine oxidase inhibiting iproniazid and phenelzine, could offer substantial benefits in what was then a rare set of disorders, variously called melancholia or endogenous depression, for which stimulants and sedatives seemed relatively unhelpful (Healy, 1997). These "antidepressant" drugs did not appear to have immediate effects, other than adverse effects. An apparently specific resolution of depressive syndromes, however, often took shape 2 or 3 weeks later.

The new treatments were known to have effects on norepinephrine (noradrenaline), cholinergic, histaminergic, and serotonergic systems. By 1961, imipramine and amitriptyline, and their derivatives desipramine and nortriptyline, were demonstrated to act on norepinephrine reuptake sites (Axelrod, 1996; Hertting & Axelrod, 1961). Inhibiting monoamine oxidase was also found to conserve levels of the catecholamines epinephrine and norepinephrine. These discoveries combined to underpin a catecholamine hypothesis of depression, according to which depression stemmed from lowered norepinephrine levels, which effective treatment restored to normal (Schildkraut, 1965, 2000).

Central neurotransmitter research began in the 1950s. Prior to that, the brain was viewed as operating electrically. Early discoveries that simple neurotransmitter defects, such as dopamine deficiency in Parkinson's disease or a defective phenylalanine hydroxylase gene in phenylketonuria, grounded hopes that, rather than nonspecific drug effects, psychiatric disorders might also be specifically remedied by magic bullets targeting simple neurotransmitter defects.

The catecholamine hypothesis called for treatments that targeted norepinephrine only. Additional actions on cholinergic, histamine, and serotonin were viewed as the source of antidepressant side effects. Pure norepinephrine reuptake inhibitors were expected to be the most effective and tolerable antidepressants (Healy, 2023a). The anticholinergic actions of imipramine and other early tricyclic antidepressants were spun as responsible for visual, urinary, bowel, balance, and cognitive problems, with the cognitive effects listed as particularly problematic (Healy, 2023a).

It quickly became clear that a simple norepinephrine deficit could not explain depression, as blocking norepinephrine reuptake happened almost immediately, while recovery took weeks. In addition, selective norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, turned out to be weaker antidepressants than imipramine and amitriptyline.

The focus switched to a norepinephrine receptor pathology. Aberrant receptors were envisaged as chunks of protein that might need weeks of chiseling back to normal, unlike the immediate effect on catecholamine levels. We now know that receptor densities and function respond to medicines nearly as quickly as transmitter levels. Despite emerging evidence of rapid receptor responses to treatment, a vision of a slow return of chemical imbalances to normal persisted (Healy, 1997).

The persistence of the notion of some chemical imbalance that medicines like selective serotonin reuptake inhibitors (SSRIs) can take weeks to correct suggests a need for a symbolic substrate to account for a slow response evident in the randomized controlled trials (RCTs) of potential antidepressants increasingly being undertaken from the 1980s onward. In the relatively severely depressed hospitalized patients being entered into trials up to 1980, these RCTs found a separation of rating scale scores on active treatment compared with placebo that became statistically significant around 2 weeks. The need for a biological linkage to slow responses became even more important with later antidepressants, as RCTs done in milder nonhospitalized depressions, owing to a relative inefficacy of these agents, commonly take 6 weeks to show some separation from placebo (Healy, 2004).

Views as to the origin of antidepressant side effects also grew more complicated by 1980. Norepinephrine reuptake inhibitors, such as duloxetine and desipramine, with no anticholinergic effects, were found to cause urinary retention, constipation, and anxiety, among other problems, while serotonergic agents cause visual, balance, sexual, and other problems (Healy, 2026). The actions of medicines that are primarily anticholinergic agents can be linked to memory problems in laboratory testing, but these cognitive changes are less marked than the memory changes linked to benzodiazepine drugs acting on gamma-aminobutyric acid systems or antipsychotic medicines acting on dopamine systems (Healy, 2023a). Moreover, although perhaps scarcely credible now, the anticholinergic effects of tricyclic antidepressants and of older primarily anticholinergic agents can be euphoriant in the correct dose, and prior to the 1965 catecholamine hypothesis, the antidepressant effect of tricyclic antidepressants had been proposed by some as the basis for the antidepressant effects of these medicines (Healy, 2023a).

ANTIDEPRESSANTS: THE UNOFFICIAL NARRATIVE

The idea of an SSRI emerged in the early 1960s from clinical observations by psychiatrists with a psychoanalytic background, who claimed that imipramine, amitriptyline, and clomipramine had beneficial cognitive or affective effects that their derivatives desipramine and nortriptyline did not have. The analysts noted a change in what they termed their patients' transference reactions, which occurred before any good or bad therapeutic response (Guyotat et al., 2000; Healy, 2002; Mayer, 1975).

Carlsson (1996), an early psychopharmacologist, linked altered transference reactions to an action on serotonin reuptake that desipramine and nortriptyline did not have. Using chlorpheniramine, a potent serotonin reuptake inhibiting antihistamine as his template, Carlsson created zimelidine, the first of what later became known as the SSRIs, an acronym coined by the marketing department of SmithKline Beecham (Healy, 2004).

The SSRI group of drugs is neither selective nor clean. Selective, as applied to SSRIs, means that drugs of this group do not work on norepinephrine systems. As might be expected from one of our most primitive neurotransmitters, dubbed a relic of marine life by Axelrod (1996), who discovered monoamine uptake (Healy, 1993), SSRIs have multiple other effects besides serotonin reuptake inhibition, such as actions on carbonic anhydrase enzymes (Poggetti et al., 2022).

In addition to the fast reuptake transporter system, serotonin and other monoamines have slow transport systems (Bönisch, 2021). Acetaminophen acts on these slow

serotonin reuptake systems and, in the process, produces many behavioral effects that overlap with SSRI effects, such as pain relief, a degree of emotional numbing, and greater risk-taking (Durso et al., 2015; Keaveney et al., 2020).

In later licensing trials, zimelidine and other SSRIs were less potent than earlier tricyclic antidepressants, with little benefit, for instance, on melancholic depressions (Healy, 2004). It became clear that the serotonergic effect was primarily an anxiolytic or serenic effect. The change in what analysts termed transference reactions is commonly described now as emotional muting, emotional blunting, or reduced emotional reactivity. This effect, like the effects of tranquilizers or beta-blocking anxiolysis, is immediate.

Two considerations led to the introduction of SSRIs as antidepressants rather than anxiolytics. First, in the 1980s, when licensing trials for these drugs were conducted, the then-dominant anxiolytics, the benzodiazepine group of tranquilizers, were increasingly linked to dependence and withdrawal (Healy, 1991). Second, a drug acting on serotonergic S-1 receptors, buspirone, branded as a non-dependence-producing serenic, had already failed to dislodge the benzodiazepines. Marketing SSRIs as antidepressants, a treatment group not linked to dependence, rather than as anxiolytics, seemed more likely to succeed (Healy, 1991).

Effective marketing, rather than superior therapeutic responses in depressive disorders compared with older agents, made the SSRIs the first-line treatment for these disorders (Healy, 2004).

Through 1990, anxiety, tension, or stress had been seen as the correct diagnostic or descriptive terms for the majority of primary care nervous problems. These conditions were not linked to a biological lesion, even in medical circles, in contrast to melancholia and manic–depressive illness. The marketing need for SSRIs, accordingly, was to convert clinical perceptions of primary care nervous problems from anxiety states to depressive illnesses, to convert cases of Valium (diazepam) into cases of Prozac (fluoxetine; Healy, 1991).

Despite their immediate serenic effect, an immediate reduction in emotional reactivity, the marketing of SSRIs as antidepressants could avail of an expectation that treatment might take weeks to demonstrate benefits. This expectation overrode perceptions of the immediate potentially beneficial effect SSRIs can have, which can be used to establish within days rather than weeks whether treatment suits a patient or not (Healy, 2026).

THERAPEUTIC PRINCIPLES

Carlsson did not view zimelidine as a magic bullet correcting an abnormality in the serotonin system. There has never been evidence of a serotonin deficit or other serotonergic problem in depression or any other mental health disorder. Taking an SSRI risks creating rather than remedying a serotonergic abnormality (Carlsson, 1996).

For Carlsson, SSRIs were a therapeutic principle that acts on a normal serotonin system, as lysergic acid diethylamide (LSD) does, which, like LSD, can produce effects beneficial for some (a good trip) and harmful for others (a bad trip). He was not surprised that some people became suicidal on an SSRI.

Depression, as this term is now used, and anxiety states comprise sets of heterogeneous conditions. In addition to condition heterogeneity, subjects in each of these

states differ physiologically and may respond differently to medicines. Thus, while most people's heart rates slow on a beta-blocking drug used as an anxiolytic, the heart rates of some speed up.

Constipation illustrates what dealing with a set of heterogeneous conditions can mean. Rather than there being one magic bullet for constipation, at least four different laxative principles may help if applied appropriately—bulk-forming, stool-softening, gut-stimulating, or gut-relaxing agents. The wrong laxative can make constipation worse. If, however, a company is licensed to use the word *laxative*, their interest is to ensure that everyone with constipation takes their laxative even if combined with other laxative principles.

Across medicine and surgery, therapeutic principles rather than magic bullets dominate. There are up to four or more therapeutic principles available to manage hypertension, diabetes, cardiac disorders, cancer, and most conditions, as well as mood disorders and other nervous problems.

Therapeutic principles also apply in psychotherapy, with Jung distinguishing between extroverts and introverts and the need for different approaches to each. It has since become clear that extroverts and introverts also differ in their responses to a range of sedative and other drugs, including SSRIs (Tranter et al., 2002). Cognitive therapy embodies a number of different principles such as cognitive restructuring, problem-solving, and behavioral activation, only one of which may be appropriate for particular patients (Jacobson et al., 1996).

A final example may bring the point home. In general, SSRIs have a greater treatment effect in obsessive–compulsive disorder (OCD) than in mood disorders (Locher et al., 2017). Alerted by clinical colleagues to patients with OCD who had a better response to smoked nicotine than to an SSRI, Carlsson ran a study in these patients that demonstrated that nicotine could be more beneficial than an SSRI for some people with OCD (Lundberg et al., 2004).

THE SSRI THERAPEUTIC PRINCIPLE

Almost all (95%) of the serotonin system on which SSRIs act is located in our bodies, not in our brains. The small amount in our brains (5%) is located in the raphe nucleus of the brain stem rather than in cortical areas. This brainstem serotonin has a role in coordinating reflex bodily functions in insects, reptiles, and humans. It is not involved in executive function or mood regulation per se.

Besides storage in platelets, where serotonin has a role in blood clotting, it is primarily located in the sensory receptors of our peripheral nervous systems. It can be found in our eyes, our vestibules, our nose, our joints, and in the sensory receptors linked to our skin and gut (which is one continuous entity). These receptors, rather than the brain, form the boundary between organisms and the world (Healy, 2026). The sensory system supports what Kahneman (2011) called our heuristic or thinking fast processes. Sensory systems are not involved in slow, problem-solving thinking.

LSD opens these sensory gates and floods our higher functions with sensations. SSRIs close these gates and mute or diminish the stream of sensory inputs. This action has some overlap in its effects with immersion in a sensory deprivation tank.

The best illustration of this sensory muting comes from the genital numbing that SSRIs produce. For most takers, genital numbing is present within an hour of the first pill given in doses often no more than 10% of the antidepressant dose (Healy, 2020). This action has been used as a therapeutic principle to manage premature ejaculation since the 1970s, and the short-acting SSRI, dapoxetine, is licensed for this purpose.

There is a similarly immediate but less obvious numbing of a range of touch modalities in our skin that correlates well with what people taking SSRIs often describe as emotional muting or numbing (Healy, 2024; Opbroek et al., 2002; Price et al., 2009). With touch, in particular, the words *sensation*, *feeling*, and *emotion* share a nexus that points to overlapping effects.

The idea that SSRIs are therapeutic principles rather than magic bullets opens a door to reconceiving their actions. A magic bullet goes to the source of the problem and eliminates or corrects it, which, in the case of a nervous problem and psychotropic drugs, suggests an action on the brain.

Therapeutic principles, in contrast, as in plates for broken bones, can aid recovery by compensating for a loss of function and need not act on the brain. In practice, many of the medicines used for mental health purposes, such as beta-blockers or benzodiazepines, offer anxiolytic benefits by slowing heart rates or relaxing muscles, which fools the brain into thinking we are not anxious to the point that calls for problem-solving. The actions of antipsychotics on conditioned avoidance responses similarly explain many of their potentially beneficial effects without a need to invoke executive function.

These actions on peripheral systems support the James–Lange theory of emotions that locates our emotions in our bodies. Our higher cognitive functions attempt to interpret our bodily intuitions and often make mistakes when attempting to do so.

Once the serotonin system is considered as a whole, the suggestion that SSRIs can be of benefit by acting on bodies, as beta-blockers and benzodiazepines do, rather than by acting as magic bullets on a specific brain locus, seems likely to be correct. The distinguishing feature of the SSRIs, compared with these other treatments, is their action on sensory systems. Despite being critical to consciousness and despite the ease of access, our sensory systems, key to a "material me," are less explored and understood than our brains (Craig, 2002; Vaitl, 1996). A common complaint from neurologists, among others, is that, unlike examining motor systems, attempts to measure sensory systems have to grapple with subjective factors.

A final point to note is that, while the effects of SSRIs on sensory receptors can be difficult to measure, patients in mental health units, blind to what is happening, can spot SSRI-linked benefits within a day or two of starting these drugs in a way medical, psychological, and nursing staff apparently cannot (Healy, 2004). How does this scotoma specifically arise in health care experts and not in others?

THERAPEUTIC PRINCIPLES AND ANTIDEPRESSANT TRIAL DATA

The serenic effects of SSRIs point to an immediate onset of effects that can be used to determine if treatment is working as designed and worth continuing with or not working as hoped and better discontinued. This vision is at odds with current mental health practice. Guidelines commonly tell patients to continue treatment for up to 6 weeks to give the treatment a chance to work, and companies have advised prescribing

a benzodiazepine or other medicine to ride out early SSRI-induced agitation until the treatment "starts" to work.

A disjunction between the needs of clinical practice and the medicines' licensing process has created this mismatch. The problem arises because, by law, studies have to take the form of RCTs, which are often held to be the gold standard for clinical evidence. Company studies, however, are better viewed as randomized controlled assays designed to obtain a license to claim that a treatment is an antidepressant rather than RCTs designed to inform clinical practice (Healy, 2023b).

The serenic effect of SSRIs is not a potent antidepressant principle. It is ineffective in severe depression. To meet regulatory requirements, SSRIs had to be tested in mildly depressed patients. Even then, 50% of the adult and pediatric licensing studies combined were negative (Healy et al., 2019; Le Noury et al., 2015; Turner et al., 2008). It took a variety of statistical stratagems, like Last Observation Carried Forward, and a sidelining of some patients, to produce, in a subset of studies, an on-average statistical benefit at 6 weeks that allowed regulators to license the use of the word antidepressant (Healy et al., 2020).

These clinically meaningless 6-week signals have unfortunately been dismissed by some as essentially placebo effects, which many understand to mean all-in-the-mind effects. Nobody having a good or bad SSRI "trip" would agree that their experience is placebo-based in this sense. These company assay data are better interpreted as demonstrating the averaging powers of an RCT process. Averaging the good and bad effects of LSD on a discrete nervous condition would likely produce a comparable failure to separate clearly from "placebo."

The apparently weak evidence for a benefit that is only reliably established at 6 weeks is neither evidence that the good or bad effects of SSRIs are weak nor evidence that these effects are not apparent within hours or days of starting, which, if recognized and used judiciously, might improve treatment outcomes.

While up to 80% of those taking an SSRI can identify a reduction in emotional reactivity (Opbroek et al., 2002), the aggregated SSRI trial data from over 100,000 subjects, held by the U.S. Food and Drug Administration, suggest that only 15% of those taking an SSRI have a markedly beneficial effect (Stone et al., 2022). In addition, approximately 50% of the trials done had an on-average negative outcome. These data point to clear responders and nonresponders. Company assay data also suggest that potentially beneficial effects are apparent in the first week of starting treatment, even in spectacularly negative trials like Study 329 (Hieronymus et al., 2016; Le Noury et al., 2015; McCafferty et al., 1997).

When a drug is licensed as an antidepressant, however, companies have spun this approval as regulatory endorsement that their drug "works"—for everyone. The capacity of the drug to produce a clear distinction between responders and nonresponders is lost.

The regulatory process clouds the clinical picture in other ways. Aware that the serenic effect of SSRIs was subtle, in order to ensure that their licensing application was successful, in company assays, SSRIs were dosed at toxic levels. Studies demonstrate that equivalent benefits could have been obtained with 5 mg rather than 20 mg of fluoxetine, for instance (Wernicke et al., 1988). The high SSRI doses, in more than fully saturating serotonin reuptake sites, verged on toxicity and required concomitant benzodiazepines to manage the resulting agitation. This antidote strategy, carried over into clinical practice,

made it more difficult to detect and use a distinct, potentially beneficial SSRI effect to guide treatment.

Similarly, a rigid adherence to the questions on a Hamilton Depression Rating Scale, the most common scale used in antidepressant assays, can produce apparent improvements in someone who is becoming actively homicidal and suicidal. Withdrawing a patient from a trial but carrying their last observation rating scale benefit forward and more generally strenuously refusing to concede that SSRIs can adversely affect takers enough to cause even healthy volunteers to commit suicide has significantly hampered clinical abilities to recognize when these drugs are not working.

In addition to the above elements, just as the heart rates of some increase on beta-blockers, some patients have no sensory muting, while other, more extraverted, patients may not appreciate this muting effect (Tranter et al., 2002).

DISCUSSION

Many, perhaps most, Nobel Prizes in medicine are won by people in a position to avail themselves of a new technology, which produces new observations leading to breakthroughs. While Carlsson (1996), benefited from new technologies, many of his breakthroughs came from listening to patients and those treating them, and a willingness to accept a drug he had created might also cause problems.

His example, especially with the SSRI group of drugs, indicates that science should not be viewed as something we follow. It is based on observations, and every giving of a medicine is an experiment that may generate new observations. New observations call for a need to achieve a consensus between the person taking the treatment, who is a privileged observer, and the person treating them, who can facilitate ways to test the combined observations of both taker and prescriber. The SSRIs demonstrate that anyone who has contact with a person on treatment can also play a role in this process.

The focus in psychotropic drug RCTs on a rating scale score as the outcome measure has another averaging effect as well. Nicotine, benzodiazepines, stimulants, neuroleptics, norepinephrine reuptake inhibitors, S-2 receptor antagonists, anticholinergic drugs, and SSRIs put into RCTs of anxiety or depressive disorders would all produce a close to indistinguishable, relatively meaningless drop in rating scale scores. RCTs like this cannot inform us how to treat patients or patients on the treatment that might suit them.

In the 1950s, before RCTs were widely used, alliances between prescribers, therapists, and patients facilitated breakthroughs and progress. Now, however, despite more treatment options, we have falling life expectancies and rising disability rates (Healy, 2021).

It is difficult to avoid the impression that something is going wrong at the interface between clinical practice, regulatory processes, and business imperatives. The official and unofficial histories of the SSRI group of drugs, outlined here, offer a telling illustration of this.

A thought experiment may illustrate the point. If a patient, at risk for an adverse reaction to an SSRI, rather than a prescription-only SSRI, takes chlorpheniramine (Chlor-Trimeton), a potent serotonin reuptake inhibitor capable of causing all serious problems SSRIs, he would be at less risk. Because if we take this over-the-counter SSRI,

guided by our observations and uninhibited by a doctor telling us these drugs can take weeks to work, we stop it if it is not suiting us.

If treatments were licensed based on their clear effects on a function, which might or might not be helpful in the management of a disorder, this could hand a degree of discretion back to physicians, other health care staff, and above all those who take the medicines. In addition to contributing to our safety, this would offer those taking medicines an opportunity to contribute observables to the scientific process to the advantage of all. This point is developed more fully in a partner article (Healy, 2026).

REFERENCES

Atigari, O., & Healy, D. (2013). Proconvulsant effects: A neglected dimension of psychotropic activity. *Australian and New Zealand Journal of Psychiatry*, *47*(11), 998–1001. https://doi.org/10.1177/0004867413495469

Axelrod, J. (1996). The discovery of amine reuptake. In D. Healy (Ed.), *The psychopharmacologists* (Vol. 1, pp. 29–50). Arnold.

Bönisch, H. (2021). Substrates and inhibitors of organic cation transporters (OCTs) and plasma membrane monoamine transporter (PMAT) and therapeutic implications. In L. C. Daws (Ed.), *Organic cation transporters in the central nervous system. Handbook of Experimental Pharmacology* (Vol. 266, pp. 119–167). https://doi.org/10.1007/164_2021_516

Carlsson, A. (1996). The rise of neuropsychopharmacology: Impact on basic and clinical neuroscience. In D. Healy (Ed.), *The psychopharmacologists* (Vol. 1, pp. 51–80).

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*(8), 655–666. https://doi.org/10.1038/nrn894

Durso, G. R. O., Luttrell, A., & Way, B. M. (2015). Over-the-counter relief from pains and pleasures alike: Acetaminophen blunts evaluation sensitivity to both negative and positive stimuli. *Psychological Science*, *26*(6), 750–758. https://doi.org/10.1177/0956797615570366

Guyotat, J., Brouillot, P., Broussolle, P., Greffe, J., Lambert, P., & Lemoine, P. (2000). The birth of psychopharmacotherapy: Explorations in a new world—1952–1968. In D. Healy (Ed.), *The psychopharmacologists* (Vol. 3, pp. 1–54). Arnold. https://doi.org/10.4324/9781003058892-1

Healy, D. (1991). The marketing of 5HT: Anxiety or depression? *British Journal of Psychiatry*, *158*, 737–742. https://doi.org/10.1192/bjp.158.6.737

Healy, D. (1993). 5-HT and physical illness. *Journal of Psychopharmacology*, *7*(1), 107–111. https://doi.org/10.1177/026988119300700101

Healy, D. (1997). *The antidepressant era*. Harvard University Press. https://doi.org/10.4%20159/9780674038455

Healy, D. (2002). *The creation of psychopharmacology*. Harvard University Press. https://doi.org/10.4159/9780674038455

Healy, D. (2004). *Let them eat Prozac*. New York University Press.

Healy, D. (2020). Antidepressants and sexual dysfunction: A history. *Journal of the Royal Society of Medicine*, *113*(4), 133–135. https://doi.org/10.1177/0141076819899299

Healy, D. (2021). *The shipwreck of the singular. Healthcare's castaways*. Samizdat Healthcare Writers' Cooperatrive.

Healy, D. (2023a). The past, present and future of anticholinergic drugs. *Therapeutic Advances in Psychopharmacology*, *13*, 1–9. https://doi.org/10.1177/20451253231176375

Healy, D. (2023b). Randomized controlled assays and randomized controlled trials: A category error with consequences. *Ethical Human Psychology and Psychiatry*, *25*(2), 119–134. https://doi.org/10.1891/EHPP-2023-0006

Healy, D. (2024). Zen and the art of moodcycle maintenance. *Ethical Human Psychology and Psychiatry*, *26*(1), 32–42. https://doi.org/10.1891/EHPP-2023-0017

Healy, D. (2026). Effects of selective serotonin reuptake inhibitors on sensory systems and mental states. *Ethical Human Psychology and Psychiatry*. https://doi.org/10.1891/EHPP-2025-0029

Healy, D, Le Noury, J., & Jureidini, J. (2019). Paediatric antidepressants: Benefits and risks. *International Journal of Risk & Safety in Medicine*, *30*(1), 1–7. https://doi.org/10.3233/JRS-180746

Healy, D., Le Noury, J., & Wood, J. (2020). *Children of the cure*. Samizdat Healthcare Writers Cooperative Press.

Hertting, G., & Axelrod, J. (1961). Fate of tritiated noradrenaline at the sympathetic nerve-endings. *Nature*, *192*, 172–173. https://doi.org/10.1038/192172a0

Hieronymus, F., Emilsson, J. F., Nilsson, S., & Eriksson, E. (2016). Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. *Molecular Psychiatry*, *21*(4), 523–530. https://doi.org/10.1038/mp.2015.53

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., Gortner, E., & Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of Consulting and Clinical Psychology*, *64*(2), 295–304. https://doi.org/10.1037//0022-006x.64.2.295

Kahneman, D. (2011). *Thinking fast and slow*. Farrar, Strauss and Giroux.

Keaveney, A., Peters, E., & Way, B. (2020). Effects of acetaminophen on risk taking. *Social Cognitive and Affective Neuroscience*, *15*(7), 725–732. https://doi.org/10.1093/scan/nsaa108

Le Noury, J., Nardo, J., Healy, D., Jureidini, J., Raven, M., Aba-Jaoude, E., & Tufanaru, C. (2015). Restoring study 329: A randomised, controlled trial of the efficacy and harms of paroxetine and imipramine in the treatment of adolescent major depression. *BMJ*, *351*, h4320. https://doi.org/10.1136/bmj.h4320

Locher, C., Koechlin, H., Zion, S. R., Werner, C., Pine, D. S., Kirsch, I., Kessler, R. C., & Kossowsky, J. (2017). Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: A systematic review and meta-analysis. *JAMA Psychiatry*, *74*(10), 1011–1020. https://doi.org/10.1001/jamapsychiatry.2017.2432

Lundberg, S., Carlsson, A., Norfeldt, P., & Carlsson, M. L. (2004). Nicotine treatment of obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *28*(7), 1195–1199. https://doi.org/10.1016/j.pnpbp.2004.06.014

Mayer, D. Y. (1975). Psychotropic drugs and the "anti-depressed" personality. *British Journal of Medical Psychology*, *48*(4), 349–357. https://doi.org/10.1111/j.2044-8341.1975.tb02341.x

McCafferty, J., Beebe, K., Gergel, I., & Broom, C. (1997). *Paroxetine study 329. Top line results*. Internal GlaxoSmithKline Document.

Opbroek, A., Delgado, O., Laukes, C., McGahuey, C., Katsanis, J., Moreno, F., & Manber, R. (2002). Emotional blunting associated with SSRI-induced sexual dysfunction. *International Journal of Neuropsychopharmacology*, *5*, 147–151. https://doi.org/10.1017/S1461145702002870

Poggetti, V., Salerno, S., Baglini, E., Barresi, E., Da Settimo, F., & Taliani, S. (2022). Carbonic anhydrase activators for neurodegeneration: An overview. *Molecules*, *27*(8), 2544. https://doi.org/10.3390/molecules27082544

Price, J., Cole, V., & Goodwin, G. M. (2009). Emotional side-effects of selective serotonin reuptake inhibitors: Qualitative study. *British Journal of Psychiatry*, *195*(3), 211–217. https://doi.org/10.1192/bjp.bp.108.051110

Schildkraut, J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of Psychiatry*, *122*(5), 509–522. https://doi.org/10.1176/ajp.122.5.509

Schildkraut, J. (2000). The catecholamine hypothesis. In D. Healy (Ed.), *The psychopharmacologists* (Vol. 3, pp. 111–134). https://doi.org/10.4324/9781003058892-4

Stone, M. B., Yaseen, Z. S., Miller, B. J., Richardville, K., Kalaria, S. N., & Kirsch, I. (2022). Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: Individual participant data analysis. *BMJ*, *378*, e067606. https://doi.org/10.1136/bmj-2021-067606

Tranter, R., Healy, H., Cattell, D., & Healy, D. (2002). Functional variations in agents differentially selective to monoaminergic systems. *Psychological Medicine*, *32*, 517–524. https://doi.org/10.1017/s0033291701005086

Turner, E. H., Matthews, A. M., Linardatos, E., Tell, R. A., & Rosenthal, R. (2008). Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine*, *358*(3), 252–260. https://doi.org/10.1056/NEJMsa065779

Vaitl, D. (1996). Interoception. *Biological Psychology*, *42*(1–2), 1–27. https://doi.org/10.1016/0301-0511(95)05144-9

Wernicke, J. F., Dunlop, S. R., Dornseif, B. E., Bosomworth, J. C., & Humbert, M. (1988). Low-dose fluoxetine therapy for depression. *Psychopharmacology Bulletin*, *24*(1), 183–188.

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