TRACING THE NEUROCHEMICAL LEGACY OF FLUOXETINE (PROZAC) IN MODERN PSYCHIATRY

[1]*Ajay,*[2]*Swarna Latha,*[3]*Sanjay kumar*
[123]*Students*
Department of Humanities & Science

ABSTRACT:
Fluoxetine, commercially known as Prozac, represents one of the most influential pharmaceuticals in the history of modern psychiatry. As the first selective serotonin reuptake inhibitor (SSRI) to gain widespread clinical use, fluoxetine revolutionized the treatment of depression, anxiety disorders, and various affective conditions. This paper explores the neurochemical foundations, pharmacodynamic mechanisms, and clinical implications of fluoxetine, tracing its legacy from its development in the 1970s to its enduring relevance in current neuropsychiatric practice.

By modulating serotonergic neurotransmission through selective inhibition of the serotonin transporter (SERT), fluoxetine enhances synaptic serotonin availability—an action central to its therapeutic efficacy. In addition to its primary mechanism, fluoxetine has been shown to exert secondary neuroplastic and anti-inflammatory effects, which contribute to its broad therapeutic profile. The drug's favorable safety margin and non-sedative profile enabled its dominance over tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

This review also highlights emerging perspectives, including fluoxetine's role in neurodevelopment, cognitive modulation, and off-label uses in conditions like premenstrual dysphoric disorder (PMDD), post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). Furthermore, we examine the societal, cultural, and ethical dimensions of fluoxetine's global impact, as it became a symbol of both hope and controversy in the treatment of mental illness.

In tracing fluoxetine's trajectory, we underscore its significance not just as a therapeutic agent, but as a scientific landmark in the chemical neuroscience of psychiatric pharmacology, offering key insights into the interplay between neurochemistry, behavior, and mental health.

I. INTRODUCTION

The latter half of the 20th century marked a transformative period in the treatment of mental health disorders, driven largely by advances in chemical neuroscience and psychopharmacology. Among the breakthroughs that reshaped psychiatric care, fluoxetine, marketed under the brand name Prozac, stands out as a cornerstone of the modern antidepressant era. Approved by the U.S. FDA in 1987, fluoxetine became the first selective serotonin reuptake inhibitor (SSRI) to enter the market, offering a safer and more tolerable alternative to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

Fluoxetine's introduction coincided with a growing awareness and destigmatization of depression and anxiety disorders, sparking widespread medical and cultural attention. Its mechanism—selectively inhibiting the serotonin transporter (SERT)—provided critical support for the monoamine hypothesis of depression, while also initiating a new wave of drug development based on neurotransmitter modulation. The drug's favorable pharmacokinetic profile, reduced side-effect burden, and non-lethality in overdose contributed to its popularity among clinicians and patients alike.

Beyond its antidepressant properties, fluoxetine's therapeutic use has since expanded to include conditions such as obsessive-compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder (PMDD). Additionally, emerging research has linked fluoxetine to neuroplasticity, neurogenesis, and potential

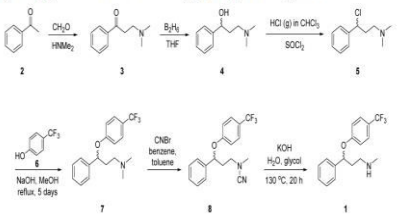
anti-inflammatory effects in the central nervous system, highlighting its broader neurochemical relevance.

This paper aims to explore the chemical and neurobiological basis of fluoxetine's action, trace its developmental history, and evaluate its impact on psychiatric treatment paradigms. By examining fluoxetine through the lens of chemical neuroscience, we not only appreciate its pharmacological significance but also gain deeper insight into how targeted modulation of neurotransmission can transform mental health care and research.

Depression is a common and recurring psychiatric syndrome, marked by episodes of low mood, poor selfesteem, and diminished interest and pleasure in most activities. Depression currently affects over 120 million people worldwide (including 1 in 10 Americans), and the number of patients diagnosed is steadily increasing at a rate of about 20% per year.1−12 The prevalence and severity of this illness leads to a correspondingly large socioeconomic impact, costing United States businesses alone over $63 billion per year as a result of low productivity, absenteeism, and treatment costs.1−14 Depression typically first manifests between the ages of 15 and 30 years, with an additional peak of onset between 30 and 45 years; however, depression can occur at any age. It is important to note that not all depression is necessarily a psychiatric disorder, as depressed mood can result from certain life events, medical treatments, and can present secondary to a nonpsychiatric illness. However, major depressive disorder (MDD) is a disabling condition that affects an individual's family, work, sleeping and eating habits, and overall health.1−14 Significantly, over 5% of patients diagnosed with MDD commit suicide, and the majority of suicides in the United States (about 60%) are carried out by patients with depression or a related mood disorder. Patients with depression often feel stigmatized and fail to seek treatment. This reticence, combined with a lack of validated biological markers for depression, likely contribute to the fact that an estimated 80% of people with symptoms of clinical depression are currently going untreated.1−14 Depression is as old as mankind, and descriptions of the disorder can be traced as far back as the Greek physician Hippocrates, who, in the fourth century, diagnosed the disorder as melancholia, (literally meaning "black bile" in Greek derived from the concept of the four humors).15 In his classic Aphorisms, Hippocrates diagnosed "fear and despondencies, if they last a long time" as melancholia. This terminology remained in medical texts and as a diagnosis until the 17th century when the term depression (from the Latin deprimere, "to press down") was employed by Delasiauve in medical texts to describe the "lowering of emotional functions". 15 This terminology eventually rose to prominence, and was formally added to the Diagnostic and Statistical Manual for Mental Disorders (DSM-I) in 1952. The designation "major depressive disorder" was added to the DSM-III in 1980.4,15 Criteria for diagnosing depression are found in the DSM-5 and World Health Organization's (WHO) ICD-10; both utilize the term "depressive episode" for singular, and "recurrent depressive disorder" for repeated depressive episodes.4,16 The ICD-10 defines three depressive symptoms (depressed mood, anhedonia and reduced energy), with two symptoms needing to be present to render the diagnosis.16 In contrast, the DSM-5 lists only two symptoms (depressed mood and anhedonia), and only one must be present for a diagnosis of depressive disorder.4 Major depressive disorder, also referred to as clinical depression, major depression, and recurrent depression, is characterized by either a single or recurrent episode of severely depressed mood that persists for at least 2 weeks.10 In addition, the DSM-5 distinguishes five subtypes of MDD: melancholic depression, atypical depression, catatonic depression, postpartum depression, and seasonal affective disorder.4 Treatment for MDD falls into three categories: psychotherapy (cognitive

behavioral therapy and interpersonal therapy), electroconvulsive therapy, and antidepressant medications.1−16 Among the medications approved to treat MDD, perhaps none is better known than fluoxetine (Prozac) 1. In this Review, we will provide an overview of the importance of 1 to the treatment of depression, as well as other CNS disorders, and will capture

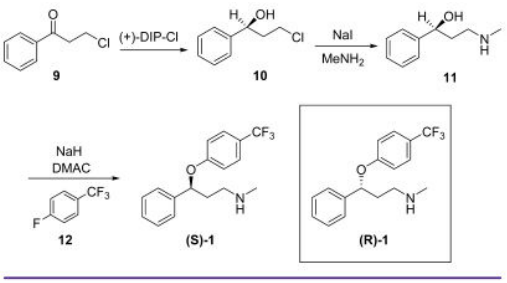
Scheme 1. Original Lilly Synthesis of Racemic Fluoxetine (1) by Molloy and Schmiegel from 1982



widely dispersed data into one easily accessible format for the "Classics in Chemical Neuroscience" series.

II. CHEMICAL SYNTHESIS

Fluoxetine, (R,S)-N-methyl-3-phenyl-3-(4-(trifluoromethyl) phenoxy)propan-1-amine (CAS No: [54910-89-3]), is a low molecular weight, racemic phenoxyphenylpropylamine (MW = 309.3) with a lone hydrogen bond donor, potentially two hydrogen bond acceptors, and a cLogP of 4.2. Thus, fluoxetine conforms to Lipinski's rules and displays excellent DMPK parameters and CNS penetration. The original synthetic route to racemic fluoxetine 1 was reported by Molloy and Schmiegel in 1982 (though filed in 1974) in US 4,314,081 (Scheme 1).17 The synthesis employed a Mannich reaction with acetophenone 2 to provide β-dimethylaminopropiophenone 3 as an oil. 3 was dissolved then dissolved in THF and added dropwise to a THF solution of 4 equiv of diborane, and allowed to stir overnight. An additional equivalent of diborane was then added and allowed to once again stir overnight. Acidic workup then provided the key racemic secondary alcohol 4. Alcohol 4 was then dissolved in CHCl3, and saturated with anhydrous HCl gas while SO2Cl was added dropwise to maintain reflux for ∼5 h. After evaporation of the solvent, 5 was collected as a crystalline hydrochloride salt. 5 was then added to an alkaline solution of 6 and refluxed for 5 days to afford phenoxy ether 7. Classical Von Braun degradation of the dimethylamino moiety, through the N-cyano derivative 8 and subsequent basic hydrolysis, provided racemic fluoxetine 1 as a free base. Importantly, the first salt form of fluoxetine (1) tested in serotonin reuptake assays in the early 1970s was the oxalate salt (LY82816); however, the marketed version is the hydrochloride salt (fluoxetine hydrochloride (LY110140), or Prozac).21 As the racemate, 1 has a published Ki of 17 nM for 5-HT uptake in rat brain synaptosomes in vitro.21 It had been previously established that the eudismic ratio (the ratio of affinities or activities of two enantiomers) of 1 is near unity (ratio of (R):(S) is 48:52).23,24 This prompted researchers at Lilly, led by Robertson, to synthesize and investigate the pharmacology of the individual (R)- and (S)-enantiomers of fluoxetine, (R)-1 and (S)-1, respectively.25 At that time, pioneering work from the Brown lab in asymmetric reduction chemistry enabled rapid access to chiral alcohols in high enantiomeric purity. In Robertson's work (Scheme 2), reduction of 3-chloro-1-phenylproan-1-one 9 with (+)-diisopinocampheylchloroborane ((+)-DIP-Cl) afforded the (S)- alcohol 10 in high enantiomeric excess (% ee). Displacement of the chloride with methylamine proved challenging, so a Scheme 2. Original Lilly asymmetric synthesis of (S)- fluoxetine, (S)-1, by Robertson from 1988



Finkelstein reaction was employed to prepare the corresponding iodide in situ, followed by displacement with methylamine to provide 11. This material was then deprotonated with NaH in DMAC, followed by the addition of 1-fluoro-4- (trifluoromethyl)benzene 12 to

deliver (S)-fluoxetine (S)-1 in a 96:4 S:R ratio. As only (+)-DIP-Cl was available, this asymmetric synthesis only allowed access to (S)-fluoxetine. In order to access (R)-fluoxetine (R)-1, Robertson and co-workers employed classical resolution techniques (fractional recrystallization) of the D- and L-mandelic acid salts of racemic 1. After conversion to the corresponding (R)-1-(1-naphthyl)ethyl ureas, HPLC and NMR confirmed that (S)-fluoxetine (S)-1 was arrived at in a >99:1 ratio of S:R enantiomers, and (R)- fluoxetine (R)-1 was arrived at in a 1.5:98.5 ratio of S:R enantiomers. Interestingly, both enantiomers were found to be essentially equipotent in vitro (Ki 's of 21 nM and 33 nM, respectively, for the (S)-1 and (R)-1), and both are equipotent in a number of in vivo preclinical models.25 This initial effort spawned numerous asymmetric syntheses of (S)-1 and (R)-1, employing more versatile catalysts that could produce both enantiomers via reduction of prochiral ketone 9. 26−28 Other asymmetric approaches installed chirality via a Sharpless asymmetric epoxidation, a Sharpless asymmetric hydroxylation, an oxidative kinetic resolution, an asymmetric carbonyl-ene reaction, or ruthenium-catalyzed allylic alkylation, to list but a few.29−33 In addition, chirality of the benzyl alcohol has also been established by enzymatic reduction and lipase-mediated enzymatic resolution.34−39 Finally, flow chemistry techniques have recently been applied to the preparation of 1. 40

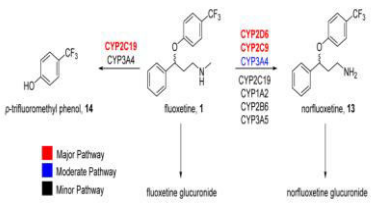


Figure 1. Structures of the oxidative and conjugative metabolites of fluoxetine 1. The major metabolite is N-desmethylfluoxetine 13, equipotent to 1, but with a significantly longer half-life. The phenolic metabolite 14 is inactive. The single enantiomers (S)-1 and (R)-1 showed divergent 2D6 metabolism.

III. MANUFACTURING INFORMATION

Fluoxetine is the generic name of the drug 1, which is manufactured by Eli Lilly & Co. under brand name Prozac (other brand names employed for fluoxetine include Zactan, Lovan, Fludac Flutine, Fluoxin, Philozac, Fluxil, Fontex, and many others).41,42 Fluoxetine was first synthesized in 1971, first disclosed in 1974 as LY110140, approved by the United States Food and Drug Administration (FDA) on December 29, 1987, and launched under the trade name Prozac in January 1988. Eli Lilly sells fluoxetine in 10, 20, and 40 mg yellow and pale-green tablets, along with a 20 mg/5 mL oral syrup.41 There are a plethora of generic manufacturers of 10−40 mg bioequivalent fluoxetine: Sandoz (approved 2001), Dr. Reddys Lab (approved 2001), Teva (approved 2002), Mylan (approved 2002), Mallinckrodt (approved 2002), Heritage Pharms (approved 2012), Alembic Pharms (approved 2009), Aurobindo Pharma (approved 2008), and many others. As of 2005, Prozac had been prescribed to more than 40 million patients worldwide and amassed over US $22 billion in sales. Annual sales peaked in 1998 with sales of US $2.8 billion; however, upon patent expiration in 2001, Eli Lilly lost US $35 million of its market value in a single day, and about 90% of Prozac prescriptions over the course of the first year with generic competition. While current sales figures for fluoxetine are difficult to ascertain precisely, worldwide sales are estimated to exceed US $400 million, with over 24 million generic prescriptions for 1 filled in 2010 in the United States and around 6 million in the United Kingdom.18−23,41,42

IV. DRUG METABOLISM

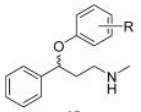
Fluoxetine 1 is almost completely absorbed following oral administration (%F = 70−90), is highly CNS-penetrant (brain/ plasma ratio in humans of 2.6:1) and possesses the largest volume of distribution (Vd) of any SSRI (between 14 and 100 L/kg).43 Fluoxetine displays low plasma protein binding (Fu = 0.05) and a long half-life (1−3 days for acute

dosing and 4−6 days upon chronic dosing). Due to the long half-life, 1 requires between 1 and 22 months to achieve steady state. Upon administration, fluoxetine 1 is subjected to significant hepatic metabolism by cytochrome P450 enzymes (CYPs) forming a number of metabolites (Figure 1), and displays nonlinear kinetics. Fluoxetine is primarily excreted (80%) as either parent 1, N-desmethylfluoxetine (norfluoxetine) 13, or as glucuronides of both 1 and 13. 43−45 The metabolites have been characterized, and while the phenolic metabolite 14 (generated via oxidative O-dealkylation by CYPs 2C19 and 3A4) is inactive, the norfluoxetine metabolite 13, generated by principally by CYP2D6 (with contributions from 2C9, 3A4, and other CYPs), possesses comparable pharmacology to 1, yet possesses a significantly longer half-life (t1/2 = 4−16 days). In fact, plasma concentrations of norfluoxetine 13 are typically 100−130% of 1, and plasma levels of both 1 and 13 can persist for more than 3 weeks after discontinuation of treatment.43−45 The key role of 2D6 in the metabolism of 1 was confirmed in humans with poor 2D6 metabolizers showing increased concentrations of 1, while extensive 2D6 metabolizers showed decreased concentrations of 1. 45 This is of special concern as 1 is both a substrate for, and inhibitor of, 2D6 and 13 is both a substrate for, and inhibitor of, 3A4. This means that 1 has significant potential to engender pharmacokinetic drug−drug interactions with atypical antipsychotics (clozapine, olanzapine, and risperidone), opiates, antidepressants (TCAs, MAOIs, and other SSRIs), and benzodiazepines.43−46 Overall, N-dealkylation is the major clearance mechanism for 1. As 1 is a racemate, interest was drawn to the metabolism of the single enantiomers (S)-1 and (R)-1. As mentioned earlier, the enantiomers are nearly equipotent at blocking serotonin reuptake, (S)-1 is only 1.5-times more potent; however, the norfluoxetine metabolite (S)-13 is 5- to 20-times more potent than (R)-13. The metabolism of (S)-1 and (R)-1 and (S)-13 is highly dependent on CYP 2D6, while that of (R)-13 is not, providing for less variable plasma concentrations of the (R)- enantiomer. A study examining the relative contributions of CYP enzymes to the metabolism of 1, (S)-1, and (R)-1 found dramatic differences.45 These data led to discovery programs between Lilly and Sepracor for the individual enantiomers. However, while pursuing (R)-1 as an antidepressant, it was found to have potential cardiotoxicity, and efforts ceased. As of 2002, efforts to pursue (S)-1 for the treatment of migraine also appear to have ceased.47,48

V. MEDICINAL CHEMISTRY, SAR, AND PHARMACOLOGY

After the antidepressant activities of TCAs were discovered, the pharmacological basis of this action was determined to be potent inhibition of monoamine uptake.49−54 Carlsson and coworkers noted that subtle structural modification among TCAs resulted in dramatic differences in serotonin (5-HT) and norepinephrine (NE) uptake in brain slices.53,54 Against this backdrop, Lilly scientists Molloy, Fuller, Rathburn, and Wong initiated a campaign to identify novel antidepressant agents lacking the side-effect profile of TCAs.17,18,21 To access novel chemical space, Molloy then employed a phenoxyphenylpropyl amine (PPA) core from which to develop analogues; moreover, Wong postulated, based on the observations of Carlsson with TCAs, that subtle structural changes within the PPA series might engender selective 5-HT uptake. Molloy then synthesized approximately 60 PPA analogues, which were found by Wong to inhibit 5-HT and/ or NE uptake in synaptosomal preparations, an activity that was confirmed in vivo by Fuller and co-workers.21,22,24 As theorized, subtle structural changes did engender dramatic variations in monoamine uptake selectivity, and Table 1 highlights key

Table 1. Structures and SAR of PPA Analogues 15[a]



15

		inhibition of uptake (K_i, nM)	
compd	R	5-HT	NE
15a	H	102	200
15b	2-OCH_3	1371	2.4
15c	2-CH_3	390	3.4
15d	2-F	898	5.3
15e	2-CF_3	1498	4467
15f	3-CF_3	166	1328
15g (1)	4-CF_3	17	2703
15h	4-CH_3	95	570
15i	4-OCH_3	71	1207
15j	4-Cl	142	568
15k	4-F	638	1276

[a]Uptake inhibition data as reported by Wong et al.[19]

structure–activity relationships (SARs). The parent PPA 15a (LY86032) was a potent 5-HT/NE uptake inhibitor (NE IC50 = 200 nM, 5-HT IC50 = 102 nM), while the addition of a 2- OMe moiety afforded 15b (LY94939, nisoxetine), a highly selective NE uptake inhibitor (NE IC50 = 2.4 nM, 5-HT IC50 =1.37 μM). Of the analogues screened, 1 (LY82816, fluoxetine oxalate) was the most potent and selective 5-HT uptake inhibitor (NE IC50 = 2.7 μM, 5-HT IC50 = 17 nM, >150-fold selective). In this same assay, the N-desmethyl metabolite norfluoxetine 13 displayed equivalent potency and selectivity to 1 (NE IC50 = 2.2 μM, 5-HT IC50 = 17 nM, >125-fold selective). From this point on, studies with 1 were performed on the HCl salt form (LY110140), and 1 was further advanced as a putative candidate.20 Despite screening only a small library of compounds by today's standards, these efforts yielded a candidate that eventually entered the therapeutic marketplace as fluoxetine (Prozac).18 The single enantiomers of fluoxetine, (S)-1 and (R)-1 also displayed comparable potencies in this assay (5-HT IC50's of 16 and 21 nM, respectively); however, the single enantiomers of norfluoxetine, (S)-13 and (R)-13, showed differential activity, with (S)-13 having a 14-fold higher potency than (R)-13 (5-HT IC50's of 20 and 268 nM, respectively). Whereas the earlier TCAs possessed significant activity at adrenergic, muscarinic, opiate, dopamine, GABA, and histamine receptors, leading to adverse events, 1 was generally clean versus these key antitargets: α1-adrenergic (21 μM), α2- adrenergic (22 μM), β-adrenergic (>10 μM), H1 (1.9 μM), M3 (6.6 μM), opiate (>10 μM), GABA (>10 μM), and D2 (2.1 μM).17−23 However, both 1 and 13 do exhibit relatively strong affinities for the 5-HT2A and 5-HT2C receptors. Over the years, numerous reports on the full pharmacology of 1 and 13 have been disclosed; however, in order to allow direct comparisons under standard assay conditions and uniform cell lines, we present recent data from the NIMH Psychoactive Drug Screening Program (Table 2).55

Table 2. Pharmacological Profile of Fluoxetine (1) and *N*-Desmethylfluoxetine (13)[a]

	K_d (nM)	
protein target	fluoxetine (1)	norfluoxetine (13)
SERT	2	38
DAT	6670	4102
NET	1560	6838
5-HT_{2A}	246	295
5-HT_{2B}	>10 000	5063
5-HT_{2C}	398	91
α_1	2262	3900
α_2	3090	>10 000
M_1	702	1200
M_2	2700	4600
M_3	1000	760
M_4	2900	2600
M_5	2700	2200
H_1	1240	>10 000
H_3	7300	>10 000

[a]K_d values as determined by the NIMH Psychoactive Drug Screening Program, http://pdsp.med.unc.edu/pdsp.php (accessed June 22, 2013).

Neurochemical studies demonstrated that, after administration of 1, extracellular 5-HT concentrations were increased 1.5- to 4-fold across multiple brain regions.56,57 In addition to heightened 5-HT concentrations, a concomitant decrease in the synthesis and release of 5-HT, as well as 5-HIAA, was observed.24 Therefore, administration of 1 appears to result in a feedback mechanism to reduce 5-HT turnover.56,57 Many reviews have focused on the preclinical behavioral pharmacology of 1; therefore, we will only list key findings here. Administration of 1 has been shown to suppress feeding, attenuate aggression, reduce amphetamine self-administration, diminish compulsive behaviors, and induce an analgesic response. Fluoxetine has shown efficacy in multiple rodent models of depression, including learned helplessness and social isolation models, as well as in the forced swim and tail suspension

tests.18,19 Interestingly, the inhibition of 5-HT uptake by 1 occurs immediately upon accessing SERT, but full antidepressant efficacy is not acquired for 3−6 weeks.58 Thus, the mechanism of action of 1 cannot be attributed exclusively to the acute elevation of 5-HT concentrations; in addition, more than 50% of preclinical studies fail to demonstrate elevated 5-HT levels after chronic administration with 1 or other SSRIs, suggesting other adaptive mechanisms.59,60 This temporal discrepancy has led to many hypotheses to account for the antidepressant activity of 1 and other SSRIs. For example, down-regulation of other 5-HT receptor subtypes, including as 5-HT1A and 5- HT2C, downstream neural adaptations, such as changes in the brain-derived neurotrophic factor (BDNF)-TrkB signaling pathway, decreases in plasma glutamate concentrations with concomitant up-regulation of forebrain glutamate receptor subunits, and increases in neurosteroid concentrations, such as 3-α-hydroxy-5-α-pregnane-2-one (3α5α-ALLO), have all been postulated to account for the efficacy of SSRIs.9,61−63 Despite years of investigation and multiple lines of thought, the exact mechanism by which fluoxetine relieves major depression symptoms is still not definitively known. Moreover, while SSRIs such as fluoxetine revolutionized the treatment of depression, they remain only partially effective, failing to relieve symptoms in >50% of depressed patients after multiple treatment regimens.

APPROVED INDICATIONS

Fluoxetine is approved for the treatment of major depressive disorder (adult and pediatric), obsessive-compulsive disorder (adult and pediatric), acute depressive episodes in Bipolar I disorder, panic disorder, bulimia nervosa, and premenstrual dysphoric disorder.41,64

ADVERSE EFFECTS AND DOSAGE

A number of adverse effects have been noted in patients taking fluoxetine. A major issue with 1 and other SSRIs concerns sexual dysfunction: erectile dysfunction, anorgasmia (inability to achieve orgasm), and diminished libido have all been well documented.41,64 However, noting the effects on anorgasmia, 1 has been used to prevent premature ejaculation.41,64 SSRIs, including 1, can elicit discontinuation syndrome, and all SSRIs carry a black box warning for increased risk of suicide (especially for patients under 25). Some studies have found that 1 and other SSRIs can lead patients to commit violent acts and display aggressive behaviors. A host of other mild side effects have been reported and include headache, nausea, drowsiness, diarrhea, tremors, photosensitivity, and weight loss.41,64 However, compared to the early TCAs and MAOIs, the side effect profile is greatly improved, especially in cases of overdose. The FDA has also approved 1 for use during pregnancy, but only recommended when the benefits outweigh the risks and is not recommended for breast-feeding mothers.1,4,13,41

HISTORY AND IMPORTANCE IN NEUROSCIENCE The earliest classes of antidepressant medications, which dominated the clinical landscape from the 1950s through the 1970s, were discovered serendipitously.65 Tricyclic antidepressants (TCAs) were developed in the 1950s in the wake of the discovery that chlorpromazine 16, derived from early synthetic antihistamines, acted as an antipsychotic agent (Figure 2).6,11,65−68 This breakthrough led to the synthesis and pharmacological evaluation of other analogues of 16, such as imipramine 17, the first TCA to be developed.69−74 Numerous efforts followed the development of 17, including the introduction of amitriptyline 18 by Merck in 1961.72−76 For many years, TCAs were the standard of care for depression.72,73 It was later discovered that TCAs exert their antidepressant affects by blocking both the serotonin transporter (SERT) and the norepinephrine transporter (NET), increasing extracellular concentrations of serotonin 19 and norepinephrine 20, with little effect on dopamine (DA) 21. 49−53,77−81 However, TCAs have promiscuous pharmacology, with

agonist or antagonist activity at multiple muscarinic, adrenergic, histamine, serotonin, and NMDA receptor subtypes, which engender significant adverse effects (e.g., agitation, dry mouth, and seizure).72,73,79 Moreover, TCAs are potent inhibitors of L-type calcium and sodium channels, leading to potentially lethal hypertension and arrhythmias.82 Thus, TCA overdose is often fatal, which limits the use of these compounds in a patient population which is at risk for suicidal behavior.

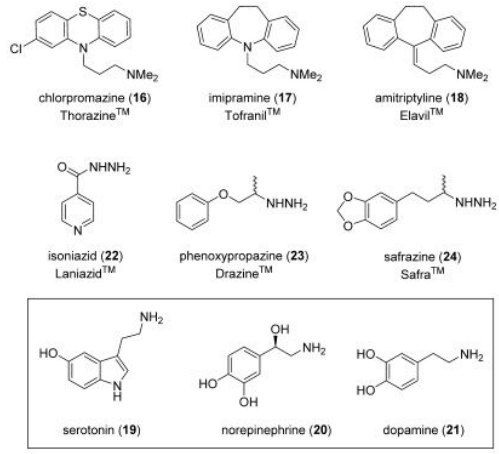


Figure 2. Structures of tricyclic antidepressants 17 and 18, and first generation nonselective, irreversible monoamine oxidase inhibitors 22−24, the first clinically available antidepressants. Also shown are the key neurotransmitters 19−21, via which these early TCAs and MAOIs elicited their antidepressant effects.

The other major class of early antidepressants, monoamine oxidase inhibitors (MAOIs), was developed out of an effort to optimize the antituberculosis drug isoniazid 22, and these compounds were only later found to possess antidepressant activity.83 This discovery led to the development of additional MAOIs, such as 23 and 24. MAOIs act to treat depression via inhibition of monoamine oxidase, which prevents the catabolism of neurotransmitters such as 19−21 (Figure 2).83−86 However, MAOIs also inhibit the breakdown of dietary amines. This can lead to hypertension if large amounts of foods containing tyramine are ingested, and can result in hyperserotonemia if large quantities of foods containing tryptophan are ingested.87−89 Moreover, these first generation MAOIs can engender serious pharmacodynamic drug−drug interactions with a wide variety of prescription and over-thecounter medications, which leads to difficulty in designing effective treatment regimens. Despite the shortcomings of TCAs and MAOIs, their apparent efficacy in the treatment of patients suffering from depression led to the development of the "monoamine hypothesis of depression". This hypothesis posits that depression results from low brain concentrations of monoamines, such as 5-HT, and catecholamines, such as NE and DA. Overall, most TCAs and MAOIs had a more robust effect on the regulation of NE than on 5-HT or DA; however, 17 and 18 were found to have a more dramatic effect on levels of 5-HT than of NE or DA.6−9,53,54 By combining this observation with clinical data, Carlsson and colleagues proposed that inhibition of 5-HT uptake may be responsible for the mood elevating profile of 17 and 18. 54 Specifically, it had been previously noted in post-mortem studies that concentrations of 5-HT, and its major metabolite 5-hydroxyindole acetic acid (5-HIAA), were found to be lower in depressed patients that committed suicide than in those patients that died from other causes.90,91 Furthermore, MAOIs were found to be more efficacious if given in combination with precursors to 5-HT synthesis.92,93

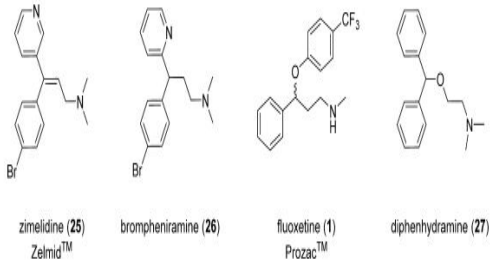


Figure 3. Structures of the first SSRIs 25 and 1, and the antihistamines 26 and 27 from which they were developed.

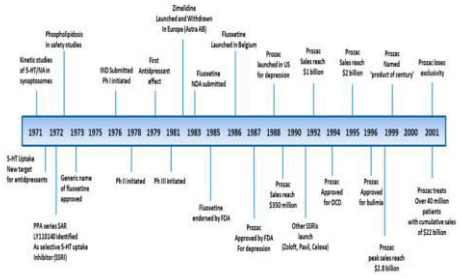
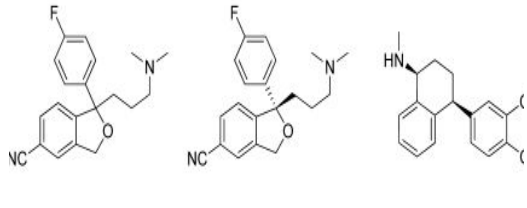


Figure 4. Timeline of the key milestones that led to the development of Prozac (1) and other SSRIs, highlighting key sales figures. Figure adapted from Wong et al.18

Finally, there were lower concentrations of 5-HIAA in bodily fluids of depressed patients than in those of healthy controls.94 Overall, this evidence pointed researchers in the early 1970s to target 5-HT reuptake as a novel therapeutic approach to treat depression. Thus, Carlsson and Astra AB developed zimelidine 25 in the 1970s, and launched this drug in Europe in 1982, making it the first selective serotonin reuptake inhibitor (SSRI) to be marketed for depression (Figure 3).95 Like the earlier TCAs, 25 was derived from an antihistamine, brompheniramine 26. Unfortunately, 25 was only on the market a short time before it was withdrawn due to induction of serious adverse events, including Guillian-Barré syndrome, a potentially fatal neuropathy.95,96 Following this, Astra AB terminated all SSRI development. Fortunately, Eli Lilly & Co. had a parallel SSRI discovery program, also based on an antihistamine, diphenhydramine 27, that ultimately produced fluoxetine 1 (Prozac). As Wong et al. detailed in a personal account of the development of fluoxetine, the road to IND and the drug that would become known as Prozac was a long, winding, and often bumpy road, replete with challenges and obstacles from within Lilly and from Lilly advisors (Figure 4).18 Shortly after a development team formed in 1973 to shepherd the product development, it was almost permanently derailed by concerns about phospholipidosis in the lungs (an excessive accumulation of phospholipids).18 During this time, Lilly scientists first disclosed 1 as an SSRI at the 1974 annual meeting of the Federation of American Societies for Experimental Biology and the American Society of Pharmacology and Experimental Therapeutics.19 In the same year, they published the SAR and pharmacology of 1 in the now seminal Life Sciences paper.21 After a 9 month delay, safety studies resumed after commentary from the Neuropharmacology division of the FDA. In 1976, 6 years after 1 was first synthesized and assayed, all of the INDenabling studies in animals were completed, and an IND was filed with the FDA.19 Later that same year, Lemberger (a Lilly clinician) first dosed 1 in humans, and 1 was found to be well tolerated in humans up to doses of 90 mg. However, in the first phase II trial in depressed patients, the drug did not differentiate from placebo, and this result almost halted the clinical development program. The basic science team was later informed that the lack of efficacy in phase II might have been due to the fact that the patients enrolled had previously failed to respond to other antidepressants.18 Thus, Lilly decided to repeat the trial with nontreatment refractory patients, but a 2 year search ensued for an appropriate clinician to oversee the trial. Slater and Stark were recruited to run the phase II and III trials with 1, and quickly provided a successful conclusion to the clinical development of fluoxetine, where it demonstrated efficacy in patients with major depression, yet lacked the undesired side effects of TCAs (blurred vision, dry mouth, and sedation) and was devoid of cardiovascular issues.18,97,98 The results were submitted to the FDA in 1983, 7 years after the first human dose of 1 was administered. At this time, Astra AB launched 25 in Europe, and the Lilly team was disappointed that they were not first to market; however, the eventual recall of 25 ultimately led to 1 being the first SSRI approved in the United States and, arguably, the most successful of the SSRIs.95,96 Yet, approval from the FDA was not rapid. Lilly did not receive approval of 1 for over 2 years after their submission, finally receiving approval on

December 29, 1987, a journey from bench to bedside of over 16 years! In January of 1988, 1, under the trade name Prozac, was launched in the United States.19



citalopram (**27**) Celexa™ escaitalopram (**28**) Lexapro™ sertaline (**29**) Zoloft™

1 was the first SSRI to be marketed in the United States, and it fundamentally changed not only the treatment of depression but also the world's perception of depression. Prozac was heralded as a safe and effective, once-daily medication for the treatment of depression with widespread adoption by physicians.

VI. CONCLUSION

Fluoxetine (Prozac) stands as a landmark discovery in the evolution of psychiatric medicine and chemical neuroscience. Its introduction as the first selective serotonin reuptake inhibitor (SSRI) not only revolutionized the treatment of depression and anxiety disorders but also transformed public and clinical perceptions of mental health. By targeting the serotonin transporter (SERT) and increasing serotonergic transmission, fluoxetine provided a safer, more targeted alternative to earlier antidepressants, with broad applicability across a range of mood, eating, and obsessive-compulsive disorders.

Beyond its immediate therapeutic uses, fluoxetine's enduring legacy lies in its role as a paradigm shift in neuropharmacology. It catalyzed a new era of research into neurotransmitter function, neuroplasticity, and the biochemical underpinnings of emotional regulation. More recent findings suggest fluoxetine may also have anti-inflammatory and neuroprotective effects, expanding its relevance to future explorations in brain health and neurodegeneration.

Yet, the drug's journey has not been without controversy—raising important discussions about overprescription, pharmaceutical marketing, and the biological reduction of complex psychological conditions. These debates, while ongoing, reflect the profound influence fluoxetine has had not just in medicine, but in culture and ethics.

As we continue to unravel the neurochemical complexities of the brain, fluoxetine remains both a clinical tool and a scientific symbol—representing the potential of targeted pharmacotherapy to reshape lives, redefine treatment paradigms, and deepen our understanding of the chemical roots of human emotion and cognition.

REFERENCES

(1) For up-to date information on depression from the National Institute of Mental Health, see: www.nimh.nih.gov/health/topics/depression.

(2) Smith, K. (2011) Trillion dollar brain drain. Nature 478, 5−8.

(3) Artigas, F. (2013) Future directions for serotonin and antidepressants. ACS Chem. Neurosci. 4, 5−8.

(4) American Psychiatric Association. (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th ed., American Psychiatric Press, Washington, DC.

(5) Lader, M. H. (1998) The Management of Depression (Checkley, S., Ed.), pp 18−211, Blackwell Press, Oxford, U.K.

(6) Glennon, R. A., and Iversen, L. (2010) Antidepressants. In Burger's Medicinal Chemistry, Drug Discovery and Development: CNS Disorders (Abraham, D. J., Rotella, D. P., Eds.), 7th ed., pp 219−264, John Wiley & Sons, Hoboken, NJ.

(7) Kessler, R. C., Chiu, W. T., Demler, O., and Walter, M. S. (2005) Prevalence, severity and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry 62, 617−627.

(8) Sullivan, P. F., Neale, M. C., and Kendler, K. S. (2000) Genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatry 157, 1552−1562.

(9) Moret, C., and Briley, M. (1992) Effect of antidepressant drugs on monamine synthesis in

brain in vivo. Neuropharmacology 31, 679−684.
(10) Culpepper, L. (2010) Why do you need to move beyond firstline therapy for major depression? J. Clin. Psychiatry 71, 4−9.
(11) Hodes, G. E., and Russo, S. J. (2012) The neurobiology of depression and anxiety: how do we change from models of drug efficacy to understanding mood and anxiety disorders? In Drug Discovery for Psychiatric Disorders (Rankovic, Z., Bingham, M., Nestler, E. J., and Hargreaves, R., Eds.), pp 159−183, The Royal Society of Chemistry, Cambridge, U.K.
(12) Metzner, R. J. (2013) The impact of neurochemical mediators on antidepressant effectiveness. ACS Chem. Neurosci. 4, 1245−1248.
(13) Gelenberg, A. G., Freeman, M. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., and Van Rhoads, R. S. (2010) Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third ed., American Psychiatric Association, Arlington, VA.
(14) For societal and workplace impact of depression, see: www. caremanagementfordepression.org.
(15) Bernois, G. E. (1998) Melancholia and depression during the 19th century: A conceptual history. Br. J. Psych. 153, 298−304.