

RESEARCH MONOGRAPH . COMPOUND PROFILE

Fluvoxamine

A 2-aminoethyl oxime ether SSRI developed at Kali-Duphar as an antidepressant and anti-obsessional agent, distinguished from other serotonin reuptake inhibitors by potent sigma-1 receptor agonism and downstream anti-inflammatory, cytoprotective, and endoplasmic reticulum chaperone activity.

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ABSTRACT

Fluvoxamine, the (E)-5-methoxy-1-[4-(trifluoromethyl)phenyl]pentan-1-one O-(2-aminoethyl)oxime, is a selective serotonin reuptake inhibitor (SSRI) of the 2-aminoethyl oxime ether structural class, first introduced in Switzerland in 1983 as Floxyfral and approved by the United States Food and Drug Administration in December 1994 for the treatment of obsessive-compulsive disorder (OCD). It is marketed in approximately 80 countries under the trade names Luvox, Fevarin, Faverin, Floxyfral, and Dumyrox for indications including OCD, social anxiety disorder (SAD), and major depressive disorder (MDD), with the extended-release formulation (Luvox CR) approved in the United States in 2008 for both OCD and SAD. Fluvoxamine is pharmacologically distinguished from the other marketed SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram) by its potent agonism at the sigma-1 receptor, a ligand-regulated endoplasmic reticulum chaperone protein, with a binding affinity (K_i approximately 36 nM) that is the highest of any clinically used SSRI and approximately 10-fold greater than that of sertraline, the next most potent sigma-1 ligand in the class [1, 2]. The sigma-1 receptor activity, formally characterized by Narita et al. (1996) and subsequently extended by multiple laboratory groups in rodent models and by Hashimoto and colleagues in translational studies, drives a pharmacological profile that extends substantially beyond serotonin reuptake inhibition: activation of the sigma-1 receptor chaperone at the mitochondria-associated endoplasmic reticulum membrane (MAM) modulates the inositol 1,4,5-trisphosphate receptor (IP3R), stabilizes the IRE1-BiP complex under endoplasmic reticulum stress,

suppresses NLRP3 inflammasome and NF-kappaB-driven proinflammatory cytokine release, and potentiates nerve growth factor-induced neurite outgrowth in neuronal cell models [3, 4, 5]. These properties have positioned fluvoxamine as a candidate for drug repositioning in inflammatory and infectious disease, most notably in the SARS-CoV-2 pandemic, where the TOGETHER trial (Reis et al. 2022) demonstrated a 32 percent relative risk reduction in the composite endpoint of emergency department retention or hospitalization among high-risk COVID-19 outpatients treated with fluvoxamine 100 mg twice daily for 10 days compared to placebo [6]. Pharmacokinetics in humans are characterized by near-complete gastrointestinal absorption, approximately 53 percent oral bioavailability due to first-pass hepatic metabolism, a plasma elimination half-life of 12 to 15 hours after single doses (extended at steady state owing to nonlinear pharmacokinetics from autoinhibition of CYP1A2 and CYP2C19), and oxidative demethylation through CYP2D6 and CYP1A2 followed by glucuronide conjugation and renal excretion [7, 8]. Fluvoxamine is itself a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP3A4 and CYP2C9, producing clinically significant drug-drug interactions with theophylline, tizanidine, alosetron, clozapine, warfarin, and ramelteon, among others [9]. The compound is well tolerated at registered doses; the principal adverse events are nausea (up to 40 percent), somnolence, insomnia, headache, and asthenia, with serotonin syndrome as a rare but serious risk in combination with other serotonergic agents or monoamine oxidase inhibitors. This monograph reviews the chemistry, synthesis, and structural class of fluvoxamine; the dual SSRI and sigma-1 receptor pharmacology in molecular and translational detail; the comprehensive human pharmacokinetic record; the clinical evidence base across OCD,

SAD, MDD, COVID-19, and investigational anti-inflammatory indications; sourcing and quality verification considerations; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five serotonergic or sigma-1-active compounds against fluvoxamine on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Fluvoxamine.

Marketed names: Luvox (United States; Solvay Pharmaceuticals, later Jazz Pharmaceuticals, later ANI Pharmaceuticals), Luvox CR (extended-release capsules; United States), Fevarin (Europe, Australia, New Zealand), Faverin (United Kingdom, Ireland), Floxyfral (Switzerland, France, several European markets), Dumyrox (several markets), Maveral (Latin America). Numerous generic formulations are available worldwide.

Development codes: DU 23000 (Kali-Duphar/Solvay internal designation). The development code appears in early pharmacology and pharmacokinetic publications from the Solvay research group [7].

Chemical Abstracts Service registry numbers: 54739-18-3 (free base), 61718-82-9 (maleate salt). The maleate salt is the formulated pharmaceutical form in all marketed preparations. The free base is the synthetic and reference standard form used in pharmacological characterization.

International Union of Pure and Applied Chemistry name: 2-[[*(E)*-(5-methoxy-1-[4-(trifluoromethyl)phenyl]pentylidene)amino]oxy]ethan-1-amine. The compound is the (*E*)-oxime ether of 5-methoxy-4'-(trifluoromethyl)valerophenone with 2-aminoethanol, a structural class distinct from the bicyclic and tricyclic scaffolds of the other SSRIs.

1.2 Structural class and chemistry

Fluvoxamine is an aralkylketone oxime ether, structurally unrelated to the diphenylamine scaffold of imipramine and the tricyclic antidepressants, the phenylpiperidine scaffold of paroxetine, the naphthylamine scaffold of sertraline, or the propylamine scaffold of fluoxetine. The compound belongs to a small structural class of monoamine reuptake inhibitors based on the 2-aminoethyl oxime ether pharmacophore, in which the oxime nitrogen serves as a bioisostere for the

amine nitrogen of conventional reuptake inhibitors and the ether oxygen provides conformational flexibility in the linker between the aromatic pharmacophore and the basic nitrogen [10].

Molecular formula: C₁₅H₂₁F₃N₂O₂ (free base); C₁₉H₂₅F₃N₂O₆ (maleate salt, 1:1).

Exact mass: 318.1555 g/mol (free base, monoisotopic).

Molecular weight: 318.33 g/mol (free base); 434.41 g/mol (maleate salt).

Physical properties: White to off-white crystalline powder. The maleate salt is freely soluble in ethanol, sparingly soluble in water (approximately 14 mg/mL at 25 degrees Celsius), and sparingly soluble in chloroform. Melting point of the maleate salt is 120 to 121 degrees Celsius. The compound has no chiral centers and exists as a single geometric isomer ((E)-configuration about the oxime C=N bond); the (Z)-isomer is a minor synthetic byproduct with substantially lower serotonin transporter affinity and is excluded from pharmaceutical-grade material by chromatographic purification.

Geometric isomerism: The oxime double bond (C=N) adopts the (E)-configuration in the active pharmaceutical ingredient, confirmed by X-ray crystallography and nuclear Overhauser effect spectroscopy. The (E)/(Z) ratio in synthetic crude is typically greater than 95:5, and pharmaceutical-grade material is specified at greater than 99 percent (E)-isomer. Investigators acquiring research-grade fluvoxamine should confirm geometric purity by HPLC or NMR if the source certificate of analysis does not specify isomeric composition.

1.3 Synthesis

The synthesis of fluvoxamine proceeds through three principal stages: Friedel-Crafts acylation of trifluoromethylbenzene with 5-methoxypentanoyl chloride (or equivalent activated carboxylic acid) to produce 5-methoxy-1-[4-(trifluoromethyl)phenyl]pentan-1-one; oximation of the ketone with hydroxylamine hydrochloride under basic conditions to produce the corresponding oxime as a mixture of (E)- and (Z)-isomers; and O-alkylation of the oxime hydroxyl with 2-chloroethylamine (or the equivalent phthalimide-protected electrophile followed by deprotection) to produce the 2-aminoethyl oxime ether [10, 11]. The (E)-isomer is separated from the (Z)-isomer by fractional crystallization or by silica gel chromatography. The maleate salt is formed by addition of maleic acid in an appropri-

ate solvent (typically ethanol or acetone) followed by recrystallization. The original patent (U.S. Patent 4,085,225, filed December 1976, issued April 1978, inventors H. B. A. Welle-van der Burg and V. Claassen, assigned to U.S. Philips Corporation) discloses the synthetic route and the (E)/(Z) separation procedure [11]. Industrial synthesis optimizes the Friedel-Crafts step for regioselectivity and the oximation step for (E)-selectivity, with overall yields of 40 to 55 percent from commercially available starting materials.

2. Abstract

Fluvoxamine (DU 23000) is a selective inhibitor of the neuronal serotonin transporter (SERT) and a potent agonist of the sigma-1 receptor, a ligand-regulated endoplasmic reticulum chaperone protein. The dual mechanism distinguishes fluvoxamine from the other marketed SSRIs and underwrites a research literature that extends substantially beyond the antidepressant and anti-obsessional indications for which the compound was developed and registered [1, 2].

The principal registered applications are the treatment of obsessive-compulsive disorder (OCD), approved by the United States FDA in December 1994 and in pediatric populations (ages 8 to 17) in 1997; the treatment of social anxiety disorder (SAD), approved for the extended-release formulation in the United States in 2008; and the treatment of major depressive disorder (MDD), approved in numerous jurisdictions outside the United States [12, 13]. In OCD, fluvoxamine at 100 to 300 mg daily produces response rates of approximately 40 to 60 percent on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), with efficacy comparable to clomipramine and the other SSRIs in meta-analytic comparisons [14, 15]. In SAD, fluvoxamine CR at 100 to 300 mg daily produces significantly greater improvement on the Liebowitz Social Anxiety Scale (LSAS) than placebo [16]. In MDD, fluvoxamine at 100 to 300 mg daily demonstrates efficacy comparable to other SSRIs and to venlafaxine in network meta-analyses, with some evidence of slightly lower efficacy relative to escitalopram and mirtazapine in head-to-head comparisons [17].

The sigma-1 receptor agonist activity, with K_i approximately 36 nM, is the pharmacological feature that has generated the most active research interest since the early 2000s. Sigma-1 receptor activation by fluvoxamine modulates endoplasmic reticulum calcium homeostasis through the IP3 receptor, stabilizes IRE1 α under ER stress conditions, suppresses NF-kappaB and NLRP3 inflammasome-driven cytokine production, and promotes neurotrophic factor signaling [3, 4, 5]. These downstream effects have provided the mechanistic rationale for repositioning studies in neuroinflammation, sepsis, acute lung injury, and viral infectious disease.

The most prominent repositioning application emerged during the SARS-CoV-2 pandemic. The TOGETHER trial (Reis et al. 2022), a randomized, placebo-controlled, adaptive platform trial conducted across 11 clinical sites in Brazil, demon-

strated that fluvoxamine 100 mg twice daily for 10 days reduced the relative risk of the composite endpoint (extended emergency department observation or hospitalization due to COVID-19) by 32 percent (relative risk 0.68; 95 percent Bayesian credible interval 0.52 to 0.88) among 741 patients randomized to fluvoxamine versus 756 to placebo [6]. The STOP COVID 2 trial and the ACTIV-6 trial, which studied lower doses (50 mg twice daily), did not demonstrate significant benefit, suggesting dose-dependent efficacy [18, 19]. The proposed mechanism involves sigma-1 receptor-mediated suppression of the cytokine amplification cascade triggered by SARS-CoV-2 infection, modulation of the IRE1-XBP1 unfolded protein response pathway exploited by viral replication, and direct anti-inflammatory effects through NLRP3 inflammasome inhibition [20, 21].

Pharmacokinetics are characterized by near-complete absorption, approximately 53 percent oral bioavailability, nonlinear dose-proportional kinetics attributable to autoinhibition of CYP1A2 and CYP2C19, and a plasma elimination half-life of 12 to 15 hours after single doses that extends to approximately 17 to 22 hours at steady state [7, 8]. The nonlinear pharmacokinetics have important practical implications for dose titration and for drug-drug interaction prediction. Fluvoxamine is the most potent CYP1A2 inhibitor among the marketed SSRIs and produces clinically significant interactions with CYP1A2 substrates including theophylline, caffeine, tizanidine, alosetron, clozapine, olanzapine, and duloxetine [9].

The compound is well tolerated at registered doses. The principal adverse events are nausea (up to 40 percent at initiation, declining with continued treatment), somnolence, insomnia, headache, asthenia, and diarrhea. Serotonin syndrome is a rare but serious risk when combined with monoamine oxidase inhibitors, other SSRIs, serotonin-norepinephrine reuptake inhibitors, triptans, or tramadol. The compound carries the class-wide boxed warning for increased suicidality risk in children, adolescents, and young adults during early treatment.

This monograph documents chemistry, synthesis, dual-mechanism pharmacology, comprehensive pharmacokinetics, the clinical evidence base across OCD, SAD, MDD, COVID-19, and investigational indications, sourcing and quality verification, reconstitution and handling, stack-interaction implications, adverse-event signal, and a structured comparative assessment of five compounds (sertraline, escitalopram, paroxetine, clomipramine, vortioxetine) against fluvoxamine on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Origin

Fluvoxamine was synthesized in the mid-1970s by researchers at Kali-Duphar, a pharmaceutical subsidiary of Solvay et Cie (later Solvay Pharmaceuticals, now part of AbbVie through the 2010 Abbott Laboratories acquisition of Solvay and the 2013 Abbott/AbbVie separation), in Weesp, the Netherlands. The compound emerged from a structure-activity relationship program exploring arylketone oxime ethers as inhibitors of neuronal monoamine reuptake, an approach chemically distinct from the tricyclic antidepressant scaffold that had dominated the preceding two decades of antidepressant medicinal chemistry [10, 11]. The synthetic and pharmacological data were first disclosed in U.S. Patent 4,085,225, filed December 23, 1976, and issued April 18, 1978, to inventors H. B. A. Welle-van der Burg and V. Claassen. Preclinical characterization in the late 1970s confirmed potent and selective inhibition of serotonin uptake in rat brain synaptosomes (IC₅₀ approximately 22 nM at the serotonin transporter), with minimal affinity for norepinephrine and dopamine transporters and negligible binding to muscarinic, histaminergic, and alpha-adrenergic receptors, a selectivity profile that foreshadowed the SSRI class concept [10].

3.2 First clinical introduction and European registration

Fluvoxamine entered clinical trials in the early 1980s and was introduced as Floxyfral in Switzerland in 1983, making it the first SSRI to reach market in any jurisdiction, preceding fluoxetine (Prozac, approved by the FDA in December 1987) by approximately four years. The initial indication was major depressive disorder. Registration followed in the United Kingdom (as Faverin), France (as Floxyfral), Germany (as Fevarin), the Netherlands, Belgium, Japan, and numerous other jurisdictions through the mid-to-late 1980s. The marketed indication in most jurisdictions was depression, with OCD added subsequently as the serotonergic hypothesis of OCD gained clinical traction [12].

3.3 United States FDA approval

Solvay Pharmaceuticals submitted a New Drug Application for fluvoxamine maleate tablets to the FDA with the proposed indication of OCD rather than depression, reflecting strategic considerations about the competitive landscape (fluoxetine, sertraline, and paroxetine had already established the SSRI class in the US depression market). The FDA approved fluvoxamine maleate tablets (25 mg, 50 mg, 100 mg; branded as Luvox) on December 5, 1994, for the treatment of obsessive-compulsive disorder in adults [12]. Pediatric OCD approval followed in 1997 for patients aged 8 to 17 years. In 2008, the FDA approved Luvox CR (extended-release capsules, 100 mg and 150 mg) for both OCD and social anxiety disorder in adults; the extended-release formulation was developed by Jazz Pharmaceuticals (formerly Elan Pharmaceuticals) under license from Solvay [13]. Fluvoxamine has never received FDA approval for major depressive disorder, though it is widely used for this indication outside the United States.

3.4 Identification of sigma-1 receptor activity

The sigma-1 receptor binding of fluvoxamine was characterized in the 1990s through radioligand displacement studies. Narita et al. (1996) reported that fluvoxamine displaced [3H](#)-pentazocine from sigma-1 receptor sites in guinea pig brain membranes with K_i approximately 36 nM, substantially higher affinity than any other SSRI tested (sertraline K_i approximately 57 nM, fluoxetine K_i approximately 240 nM, paroxetine K_i greater than 1000 nM, citalopram K_i greater than 1000 nM) [1]. Ishima et al. (2014) extended this characterization with positron emission tomography using [^{11}C]SA4503 and demonstrated that oral fluvoxamine at therapeutic doses produced measurable sigma-1 receptor occupancy in the intact human brain, confirming the translational relevance of the in vitro binding data [22]. These findings initiated a research trajectory that repositioned fluvoxamine as a pharmacological tool for investigating sigma-1 receptor biology and as a clinical candidate for sigma-1-mediated indications beyond depression and OCD.

3.5 COVID-19 repositioning

The SARS-CoV-2 pandemic in 2020 catalyzed rapid repositioning efforts for approved medications with anti-inflammatory or antiviral properties. Lenze et al. (2020) published the first randomized clinical trial of fluvoxamine for COVID-19 (the STOP COVID trial), a 152-patient double-blind study demonstrating that fluvox-

amine 100 mg three times daily for 15 days reduced clinical deterioration compared to placebo [23]. The larger TOGETHER trial (Reis et al. 2022), with 1497 patients, confirmed the clinical benefit at 100 mg twice daily and established fluvoxamine as one of the few repurposed oral agents with positive randomized trial evidence for early COVID-19 treatment [6]. The mechanistic basis was attributed to sigma-1 receptor-mediated anti-inflammatory effects, particularly through modulation of the IRE1-XBP1 pathway and suppression of cytokine amplification [20, 21].

4. Mechanism of Action

Fluvoxamine is a dual-mechanism agent. Its principal molecular activities, characterized in heterologous expression systems, native tissue preparations, and behavioral models, are inhibition of the serotonin transporter (SERT) and agonism at the sigma-1 receptor. These activities operate at concentrations achieved by therapeutic oral doses and contribute differentially to the antidepressant, anti-obsessional, anxiolytic, and anti-inflammatory effects.

4.1 Serotonin transporter inhibition

The serotonin transporter (SERT, SLC6A4) is a sodium- and chloride-dependent monoamine transporter expressed on presynaptic serotonergic neurons throughout the central and peripheral nervous systems. It mediates the reuptake of serotonin (5-hydroxytryptamine, 5-HT) from the synaptic cleft into the presynaptic terminal, terminating serotonergic neurotransmission. Fluvoxamine binds the SERT with high affinity (K_i approximately 2 to 10 nM in human platelet and rat brain synaptosomal preparations) and inhibits serotonin reuptake with an IC_{50} of approximately 22 nM [10, 24]. The inhibition is selective: affinity for the norepinephrine transporter (NET) is approximately 1000-fold lower (K_i approximately 1300 nM), and affinity for the dopamine transporter (DAT) is negligible (K_i greater than 10,000 nM) [10].

The selectivity profile distinguishes fluvoxamine from the tricyclic antidepressants (which inhibit both SERT and NET and bind muscarinic, histaminergic, and alpha-adrenergic receptors) and positions it within the SSRI class. Among the SSRIs, fluvoxamine has moderate SERT potency; paroxetine and escitalopram are more potent SERT inhibitors by approximately 2- to 5-fold in most assay systems, while fluoxetine and sertraline are broadly comparable [24].

The therapeutic consequences of SERT inhibition are enhanced serotonergic neurotransmission, particularly in the raphe-cortical and raphe-limbic projections, leading to the antidepressant, anti-obsessional, and anxiolytic effects that constitute the registered indications. The onset of therapeutic effect (typically 2 to 6 weeks) is longer than the onset of SERT occupancy (which approaches near-maxi-

mal levels within days at therapeutic doses), reflecting the downstream neuroplastic adaptations (5-HT1A autoreceptor desensitization, BDNF upregulation, hippocampal neurogenesis) that are the proximate mediators of clinical response [25].

4.2 Sigma-1 receptor agonism

The sigma-1 receptor is a 223-amino acid transmembrane protein residing primarily at the mitochondria-associated endoplasmic reticulum membrane (MAM). It functions as a ligand-regulated molecular chaperone that interacts with multiple client proteins, including the inositol 1,4,5-trisphosphate receptor type 3 (IP3R3), the IRE1alpha kinase/endonuclease, the voltage-gated potassium channel Kv1.2, and the acid-sensing ion channel ASIC1a [2, 3]. In its resting state, the sigma-1 receptor is bound to the immunoglobulin heavy chain binding protein (BiP/GRP78), an ER chaperone. Upon ligand binding, the sigma-1 receptor dissociates from BiP and becomes available to chaperone its client proteins, modulating calcium signaling, ER stress responses, and inflammatory cascades.

Fluvoxamine binds the sigma-1 receptor with K_i approximately 36 nM, the highest affinity of any clinically used SSRI [1, 2]. The binding is agonistic: fluvoxamine promotes dissociation of the sigma-1 receptor from BiP, enhances sigma-1 receptor chaperone activity at the MAM, potentiates IP3R-mediated calcium release from the ER, and stabilizes the IRE1alpha-BiP complex under ER stress conditions, thereby attenuating the unfolded protein response and downstream apoptotic signaling [3, 4].

The downstream consequences of sigma-1 receptor activation by fluvoxamine include:

Neurotrophic effects. Fluvoxamine potentiates nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells through sigma-1 receptor-dependent mechanisms, an effect blocked by the selective sigma-1 receptor antagonist NE-100 and not reproduced by SSRIs with low sigma-1 affinity (paroxetine, citalopram) [5]. The neurotrophic activity is plausibly mediated by sigma-1 receptor-dependent enhancement of phospholipase C-gamma, IP3 receptor, and calcium/calmodulin-dependent signaling cascades.

Anti-inflammatory effects. Sigma-1 receptor activation suppresses NF-kappaB-driven proinflammatory cytokine release (TNF-alpha, IL-1beta, IL-6) and inhibits NLRP3 inflammasome assembly in macrophages and microglial cells [4, 26].

Fluvoxamine attenuates endotoxin-induced acute lung injury in murine models through sigma-1 receptor-dependent pathways, reducing neutrophil infiltration, pulmonary edema, and proinflammatory cytokine levels [27].

ER stress modulation. Under conditions of ER stress (triggered by thapsigargin, tunicamycin, or viral protein accumulation), fluvoxamine-mediated sigma-1 receptor activation stabilizes the IRE1alpha endonuclease in its active state while preventing excessive PERK and ATF6 activation, thereby promoting adaptive (pro-survival) rather than maladaptive (pro-apoptotic) ER stress signaling [3, 20].

Antiviral considerations. The sigma-1 receptor has been identified as a host factor exploited by several RNA viruses, including SARS-CoV-2, for modulation of the ER stress and autophagy pathways required for viral replication. Gordon et al. (2020) identified sigma-1 receptor as a high-confidence interactor of the SARS-CoV-2 NSP6 protein in a comprehensive host-virus protein-protein interaction map [21]. Fluvoxamine's sigma-1 agonism is hypothesized to interfere with this interaction and to reduce the cytokine amplification that drives severe COVID-19 pathology. The precise contribution of sigma-1 receptor modulation versus the anti-inflammatory effects of fluvoxamine in COVID-19 remains an area of active investigation.

4.3 Receptor selectivity profile

Fluvoxamine has negligible affinity (K_i greater than 1000 nM) for muscarinic acetylcholine receptors (M1 through M5), histamine H1 receptors, alpha-1 and alpha-2 adrenergic receptors, dopamine D1 through D5 receptors, GABA-A receptors, and opioid receptors [10, 24]. This selectivity profile accounts for the relatively low incidence of anticholinergic effects (dry mouth, urinary retention, constipation), sedation, orthostatic hypotension, and weight gain compared to the tricyclic antidepressants. Among the SSRIs, fluvoxamine has the lowest muscarinic receptor affinity and one of the lowest histamine H1 affinities, contributing to its favorable tolerability profile for anticholinergic and sedative side effects.

4.4 Composite pharmacology at therapeutic doses

At the registered dose range of 100 to 300 mg daily, fluvoxamine achieves steady-state plasma concentrations of approximately 100 to 400 ng/mL (approximately 0.3 to 1.3 micromolar) [7, 8]. At these concentrations, SERT occupancy exceeds 80 percent (consistent with PET imaging studies with [^{11}C]DASB demonstrating near-

maximal transporter occupancy at doses above 50 mg daily), and sigma-1 receptor occupancy is substantial (confirmed by [11C]SA4503 PET showing dose-dependent sigma-1 receptor binding in human brain at therapeutic fluvoxamine doses) [22, 28]. The dual occupancy at therapeutic concentrations supports the clinical relevance of both mechanisms and distinguishes fluvoxamine from SSRIs that achieve SERT occupancy but not sigma-1 receptor occupancy at their respective therapeutic doses (paroxetine, citalopram, escitalopram).

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Fluvoxamine maleate is almost completely absorbed from the gastrointestinal tract after oral administration. The extent of absorption is not significantly affected by food, although the rate of absorption may be slightly delayed [7]. Oral bioavailability is approximately 53 percent, the reduction from complete absorption attributable to first-pass hepatic metabolism. Peak plasma concentration (C_{max}) is reached at approximately 3 to 8 hours after administration of immediate-release tablets and 4 to 12 hours after administration of extended-release capsules. After a single 100 mg oral dose, C_{max} is approximately 31 to 88 ng/mL in healthy volunteers, with substantial interindividual variability reflecting CYP polymorphism and other pharmacogenomic factors [7, 8].

5.2 Distribution

The volume of distribution after intravenous administration is approximately 25 L/kg, indicating extensive tissue distribution. Plasma protein binding is approximately 77 percent, predominantly to albumin. The compound crosses the blood-brain barrier; cerebrospinal fluid concentrations approximate 70 to 80 percent of free plasma concentrations. Central nervous system distribution is confirmed by PET studies demonstrating SERT and sigma-1 receptor occupancy at therapeutic doses [22, 28].

5.3 Metabolism

Fluvoxamine is extensively metabolized in the liver by oxidative demethylation and deamination. The principal metabolic pathways are: (a) oxidative demethylation of the 5-methoxy group, mediated primarily by CYP2D6, producing the O-demethylated metabolite; (b) oxidative deamination of the aminoethyl side chain; and (c) subsequent conjugation (glucuronidation) of the resulting metabolites.

Approximately nine metabolites have been identified in human urine, none with significant pharmacological activity at the serotonin transporter or sigma-1 receptor [7, 8, 29].

The pharmacokinetics of fluvoxamine are nonlinear. At doses above 50 mg, plasma concentrations increase disproportionately with dose. The mechanism of nonlinearity is not classical Michaelis-Menten saturation of a single metabolic pathway but rather autoinhibition: fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19, and at higher doses, the accumulated parent compound inhibits its own metabolism through these enzymes, producing supraproportional increases in plasma exposure [8, 29]. This nonlinearity has practical implications: doubling the dose from 100 to 200 mg may produce more than a doubling of steady-state plasma concentration, and dose titration should proceed cautiously.

5.4 Elimination

The plasma elimination half-life is approximately 12 to 15 hours after a single oral dose in healthy volunteers and extends to approximately 17 to 22 hours at steady state, reflecting the autoinhibition-mediated nonlinear kinetics [7, 8]. Steady state is achieved within 7 to 10 days of constant daily dosing. Approximately 94 percent of an administered dose is recovered in urine as metabolites; less than 2 percent is excreted unchanged. Fecal excretion accounts for a minor fraction.

Renal impairment has minimal effect on fluvoxamine pharmacokinetics given the predominantly hepatic metabolic clearance. Hepatic impairment significantly prolongs elimination and reduces clearance; dose reduction is recommended in patients with hepatic insufficiency. In elderly subjects, clearance is reduced by approximately 50 percent compared to young adults, and lower starting doses are recommended [30].

5.5 Routes of administration

The only clinically registered route is oral. Fluvoxamine maleate is supplied as immediate-release tablets (25 mg, 50 mg, 100 mg) and as extended-release capsules (100 mg, 150 mg). No intravenous, intramuscular, or subcutaneous formulations are marketed. The immediate-release tablets are typically administered once daily at bedtime (at lower doses) or in divided doses (at higher doses, to reduce nausea),

while the extended-release capsules are administered once daily at bedtime. For research applications, the compound is available as the maleate salt powder for preparation of oral solutions or for in vitro and in vivo experimental use.

5.6 Special populations

Pediatric pharmacokinetics have been characterized in children aged 6 to 17 years. Steady-state plasma concentrations in children are approximately 2- to 3-fold higher than in adults at equivalent milligram-per-kilogram doses, attributable to lower CYP1A2 activity in prepubertal children [30]. Dose adjustment is required. Geriatric pharmacokinetics are characterized by approximately 50 percent reduction in clearance; lower starting doses and slower titration are recommended. Pregnancy data are limited; the compound is classified as FDA pregnancy category C (animal reproduction studies have shown adverse effects, and there are no adequate and well-controlled studies in humans). Neonatal withdrawal syndrome has been reported in infants exposed to fluvoxamine in the third trimester. Use in lactation: fluvoxamine is excreted in human breast milk; the estimated infant dose is less than 2 percent of the maternal weight-adjusted dose, which is generally considered compatible with breastfeeding under close monitoring [31].

6. Preclinical Pharmacology

6.1 Serotonergic activity in vitro and in vivo

Fluvoxamine inhibits serotonin uptake in rat brain synaptosomes with an IC₅₀ of approximately 22 nM and in human platelet preparations with comparable potency [10]. In the microdialysis paradigm, systemic administration of fluvoxamine (10 to 30 mg/kg intraperitoneally in rats) produces approximately 3- to 5-fold elevations in extracellular serotonin concentrations in the frontal cortex and hippocampus, with minimal effects on extracellular norepinephrine and dopamine [10, 24]. These neurochemical effects translate to behavioral activity in the forced swim test, tail suspension test, and chronic mild stress paradigm, standard rodent models of antidepressant-like activity.

6.2 Sigma-1 receptor-mediated neuroprotection

In PC12 pheochromocytoma cells, fluvoxamine at 1 to 10 micromolar potentiates NGF-induced neurite outgrowth by approximately 40 to 60 percent, an effect abolished by NE-100 (sigma-1 receptor antagonist) and not reproduced by paroxetine or citalopram at equivalent concentrations [5]. In primary cortical neuronal cultures, fluvoxamine protects against thapsigargin-induced ER stress and apoptosis through sigma-1 receptor-dependent stabilization of the IRE1 α -BiP complex [3]. In the cuprizone model of demyelination in mice, fluvoxamine (20 mg/kg/day for 5 weeks) promoted oligodendrogenesis from neural stem cells and attenuated demyelination and inflammatory cytokine expression [26].

6.3 Anti-inflammatory activity

Rosen et al. (2019) demonstrated that fluvoxamine (but not other SSRIs lacking sigma-1 receptor affinity) suppressed lipopolysaccharide-induced IL-6, TNF- α , and IL-1 β production in bone marrow-derived macrophages through sigma-1 receptor-IRE1 pathway modulation [4, 27]. In a murine cecal ligation and puncture model of sepsis, fluvoxamine (20 mg/kg intraperitoneally) improved survival and reduced serum cytokine levels. In an endotoxin-induced acute lung injury model,

fluvoxamine reduced neutrophil infiltration, alveolar protein leakage, and proinflammatory mediator production [27]. These preclinical findings provided the mechanistic foundation for the COVID-19 clinical trials.

6.4 Acid sphingomyelinase inhibition

Fluvoxamine, along with several other cationic amphiphilic drugs, has been characterized as a functional inhibitor of acid sphingomyelinase (FIASMA), an enzyme that catalyzes the hydrolysis of sphingomyelin to ceramide in the endolysosomal compartment [32]. Ceramide-enriched membrane platforms facilitate SARS-CoV-2 cell entry; inhibition of acid sphingomyelinase by fluvoxamine may therefore represent an additional mechanism contributing to the observed antiviral effects in COVID-19, independent of the sigma-1 receptor pathway.

7. Clinical Evidence Base

7.1 Obsessive-compulsive disorder

OCD is the principal registered indication for fluvoxamine in the United States. The pivotal registration trials demonstrated that fluvoxamine at 100 to 300 mg daily produced statistically significant and clinically meaningful reductions in Y-BOCS scores compared to placebo over 8 to 12 weeks of treatment [14]. Response rates (defined as 25 to 35 percent reduction in Y-BOCS total score) ranged from 40 to 60 percent across trials, compared to 15 to 30 percent on placebo.

Meta-analytic comparisons place fluvoxamine broadly equivalent to clomipramine and the other SSRIs (fluoxetine, sertraline, paroxetine, escitalopram) in OCD efficacy, with no consistent superiority of any individual agent [15, 32]. A 2025 comprehensive meta-analysis encompassing 16 studies and 1745 OCD patients across five systematic reviews confirmed that fluvoxamine is significantly superior to placebo and comparable to other serotonergic agents in OCD symptom reduction [33]. One recent randomized controlled trial reported fluvoxamine to be more effective than sertraline in reducing OCD symptoms, though this finding requires replication [34].

The dose-response relationship in OCD favors higher doses. Meta-analytic data from the Bloch et al. (2010) dose-response analysis of SSRIs in OCD found that higher SSRI doses (within the approved range) were associated with significantly greater efficacy, supporting the clinical practice of titrating to the maximum tolerated dose in OCD [35].

Pediatric OCD data support efficacy in children aged 8 to 17 years at doses of 50 to 200 mg daily, with the 1997 FDA approval based on a multicenter placebo-controlled trial demonstrating significant Y-BOCS-C score reduction [36].

7.2 Social anxiety disorder

Fluvoxamine CR (extended-release capsules) received FDA approval for SAD in 2008 based on two multicenter, randomized, double-blind, placebo-controlled trials. In pooled analyses, fluvoxamine CR at 100 to 300 mg daily produced significantly

greater improvement on the LSAS total score and the CGI-Severity scale compared to placebo, with response rates (CGI-Improvement of 1 or 2) of approximately 40 to 50 percent versus 20 to 30 percent on placebo [16].

A meta-analysis by Irons (2005) evaluating fluvoxamine in SAD across multiple studies confirmed that fluvoxamine significantly outperformed placebo on LSAS scores and CGI measures, with a mean effect size consistent with the other SSRIs approved for SAD [37]. The immediate-release formulation also demonstrated efficacy in SAD in a pivotal study by Stein et al. (1999), a 92-patient double-blind placebo-controlled trial reporting significantly greater LSAS improvement with fluvoxamine 150 mg daily [38].

7.3 Major depressive disorder

Fluvoxamine was the first SSRI introduced for the treatment of MDD (Switzerland, 1983) and is approved for this indication in the majority of jurisdictions outside the United States. Efficacy in MDD is well established through numerous placebo-controlled trials and active-comparator studies accumulated over more than four decades [17].

In network meta-analyses comparing the SSRIs and other antidepressants, fluvoxamine demonstrates efficacy comparable to other SSRIs and to the serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine) for acute MDD treatment [17]. The Cipriani et al. (2009) network meta-analysis of 117 randomized controlled trials and 25,928 patients found that fluvoxamine was significantly less effective than escitalopram and mirtazapine and less well tolerated than escitalopram, sertraline, and citalopram, placing fluvoxamine in the middle tier of the antidepressant efficacy-tolerability matrix [39]. A subsequent Cipriani et al. (2018) update of 522 trials largely confirmed these relative rankings [40].

Fluvoxamine demonstrates particular utility in MDD with comorbid anxiety symptoms. Ottevanger (1994) reported that 60 percent of patients with MDD and comorbid anxiety disorders showed significant improvement on both anxiety and depression measures after 6 weeks of fluvoxamine treatment [41].

7.4 COVID-19

The SARS-CoV-2 pandemic generated three principal randomized controlled trials of fluvoxamine for early outpatient COVID-19 treatment:

STOP COVID (Lenze et al. 2020). A double-blind, randomized, placebo-controlled trial of 152 symptomatic adult outpatients with confirmed COVID-19. Fluvoxamine 100 mg three times daily for 15 days. Zero of 80 fluvoxamine-treated patients experienced clinical deterioration (defined as dyspnea, hospitalization, or oxygen saturation below 92 percent) compared to 6 of 72 placebo patients (8.3 percent). The difference was statistically significant (log-rank $p = 0.009$) [23].

TOGETHER trial (Reis et al. 2022). A randomized, placebo-controlled, adaptive platform trial conducted across 11 sites in Brazil. 741 patients randomized to fluvoxamine 100 mg twice daily for 10 days; 756 to placebo. The composite primary endpoint (emergency department retention for greater than 6 hours or hospitalization due to COVID-19 within 28 days) occurred in 11 percent of the fluvoxamine group versus 16 percent of the placebo group (relative risk 0.68; 95 percent Bayesian credible interval 0.52 to 0.88). The trial was stopped for superiority [6].

STOP COVID 2 (McCarthy et al. 2023). A multicenter, double-blind, randomized, placebo-controlled trial of 547 adult outpatients. Fluvoxamine 50 mg twice daily for 15 days. No significant difference in the primary composite endpoint of hospitalization, emergency department visit, or death. The lower dose (50 mg twice daily versus 100 mg twice daily in TOGETHER) is the principal methodological difference and the most likely explanation for the negative result [18].

ACTIV-6 (Stewart et al. 2023). A decentralized, double-blind, randomized, placebo-controlled platform trial. Fluvoxamine 50 mg twice daily for 10 days. No significant benefit on the primary outcome of time to sustained recovery. Again, the lower dose is the principal difference from the positive TOGETHER trial [19].

A 2022 meta-analysis of the randomized controlled trial data concluded that fluvoxamine at 100 mg twice daily or higher demonstrates a statistically significant reduction in COVID-19 clinical deterioration, while the 50 mg twice daily dose does not [42]. The dose-response pattern is consistent with the sigma-1 receptor occupancy data, which predict meaningful receptor engagement only at doses producing plasma concentrations in the low-micromolar range [22].

7.5 Other investigational indications

Post-traumatic stress disorder (PTSD). Open-label and small controlled studies have reported benefit of fluvoxamine in PTSD symptoms, though evidence is insufficient for registration and the compound is not included in major PTSD treatment

guidelines [43].

Panic disorder. Fluvoxamine has demonstrated efficacy in panic disorder with or without agoraphobia in controlled trials at 100 to 300 mg daily, though it is not registered for this indication in most jurisdictions [44].

Premenstrual dysphoric disorder (PMDD). Limited trial data support intermittent (luteal-phase) fluvoxamine at 50 to 100 mg daily for PMDD symptoms, with efficacy comparable to other SSRIs used for this indication [45].

Neuroinflammatory conditions. Preclinical studies demonstrate that fluvoxamine attenuates lipopolysaccharide-induced neuroinflammation, endotoxin-induced acute lung injury, and sepsis-related organ damage through sigma-1 receptor-dependent mechanisms in murine models [26, 27]. Clinical translation to specific neuroinflammatory indications beyond COVID-19 remains investigational.

8. Sourcing and Quality Verification

Pharmaceutical-grade fluvoxamine maleate is widely available as the generic tablet formulation in the United States, Europe, Japan, and numerous other jurisdictions. The compound is off-patent; multiple generic manufacturers supply 25 mg, 50 mg, and 100 mg immediate-release tablets and 100 mg and 150 mg extended-release capsules. Pharmaceutical-grade sourcing is the highest quality option for clinical research applications.

Research-grade fluvoxamine maleate is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich/MilliporeSigma, Tocris Bioscience, Cayman Chemical, MedChemExpress, TCI, Selleckchem, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to multi-gram quantities as the maleate salt. The free base is available from some suppliers but is less commonly used. Pricing is moderate, typically in the range of \$20 to \$100 per gram of research-grade material.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (319.16 +/- 0.01 for the protonated free base [M+H]⁺; 435.17 +/- 0.01 for the protonated maleate salt)
- Nuclear magnetic resonance spectroscopy (¹H and ¹⁹F NMR) confirmation of structure and (E)-isomer geometric purity
- Karl Fischer or loss-on-drying analysis for residual water content
- Melting point determination (120 to 121 degrees Celsius for the maleate salt)

The research-grade fluvoxamine market is well established given the compound's long history and generic availability. Counterfeit or degraded material is uncommon, but lot-to-lot variability in geometric purity ((E)/(Z) ratio) and residual solvent content is possible. On-receipt analytical confirmation is appropriate for mechanistic studies where sigma-1 receptor activity or SERT binding precision is important.

9. Reconstitution and Handling

Fluvoxamine maleate is sparingly soluble in water (approximately 14 mg/mL at 25 degrees Celsius) and freely soluble in ethanol. For research applications, stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO) for in vitro studies or at 1 to 10 mg/mL in physiological saline or phosphate-buffered saline for in vivo studies.

Storage of the solid powder is recommended at room temperature (15 to 25 degrees Celsius) in a dry, light-protected environment. The compound is stable under these conditions for at least 2 years. DMSO stock solutions should be stored at minus 20 degrees Celsius, protected from light, and are stable for at least 6 months. Aqueous solutions should be prepared fresh or stored at 2 to 8 degrees Celsius and used within 7 days.

Repeated freeze-thaw cycles should be minimized. Aliquoting of stock solutions into single-use volumes is recommended. The compound is not light-sensitive under normal laboratory conditions, but prolonged exposure to ultraviolet radiation may promote (E)-to-(Z) isomerization; light protection is therefore reasonable practice for stored solutions.

For oral administration in clinical research, the commercially available immediate-release tablets can be crushed and suspended in water or administered intact. The extended-release capsules should not be crushed, as the controlled-release coating is integral to the pharmacokinetic profile.

10. Stack Interaction Considerations

Fluvoxamine has a clinically significant drug interaction profile driven primarily by its potent inhibition of CYP1A2, CYP2C19, and (to a lesser extent) CYP3A4 and CYP2C9. Investigators conducting research with fluvoxamine, especially in combination with other research compounds or in populations receiving concurrent medications, should consider:

CYP1A2 substrates: Fluvoxamine is the most potent CYP1A2 inhibitor among the marketed SSRIs. Concurrent administration with CYP1A2 substrates can produce clinically dangerous elevations in substrate exposure. Specific contraindicated or cautioned combinations include [9]:

- Theophylline: approximately 3-fold increase in theophylline AUC. Dose reduction required.
- Tizanidine: approximately 33-fold increase in tizanidine AUC. Coadministration is contraindicated.
- Alosetron: approximately 6-fold increase in alosetron AUC. Coadministration is contraindicated.
- Clozapine: approximately 5- to 10-fold increase in clozapine levels. Risk of seizures and hypotension.
- Olanzapine: 2- to 3-fold increase in olanzapine AUC. Dose adjustment required.
- Caffeine: approximately 5-fold increase in caffeine half-life. Clinical significance depends on intake.
- Duloxetine: approximately 6-fold increase in duloxetine AUC. Coadministration is generally avoided.
- Ramelteon: approximately 190-fold increase in ramelteon AUC. Coadministration is contraindicated.

CYP2C19 substrates: Fluvoxamine is a potent CYP2C19 inhibitor. Relevant interactions include diazepam (prolonged elimination, consider dose reduction), omeprazole (2- to 5-fold increase in AUC), phenytoin (increased levels, monitoring required), and clopidogrel (reduced bioactivation of the prodrug, potential clinical relevance under investigation) [9].

CYP3A4 substrates: Moderate inhibition. Relevant interactions include alprazolam (approximately 2-fold increase in AUC, dose reduction required), carbamazepine, and selected statins metabolized primarily by CYP3A4.

Serotonergic agents: Concurrent use with monoamine oxidase inhibitors (MAOIs) is absolutely contraindicated due to the risk of life-threatening serotonin syndrome. A washout period of at least 14 days is required between discontinuation of an MAOI and initiation of fluvoxamine, and at least 14 days between discontinuation of fluvoxamine and initiation of an MAOI. Concurrent use with other SSRIs, SNRIs, triptans, tramadol, lithium, St. John's wort, or tryptophan increases serotonin syndrome risk and should be approached with caution [9].

Warfarin and anticoagulants: Fluvoxamine increases warfarin plasma concentrations (predominantly the R-enantiomer) through CYP1A2 and CYP2C9 inhibition. INR monitoring is required during coadministration. SSRIs as a class also impair platelet aggregation through serotonin depletion from platelets, increasing bleeding risk independently of the pharmacokinetic interaction.

Benzodiazepines: Alprazolam and diazepam undergo increased exposure during fluvoxamine coadministration through CYP3A4 and CYP2C19 inhibition respectively. Lorazepam and oxazepam, which are metabolized by direct glucuronidation rather than CYP enzymes, are preferred concurrent benzodiazepines when fluvoxamine is prescribed.

Melatonin and melatonin agonists: Fluvoxamine markedly increases melatonin levels through CYP1A2 inhibition and has been reported to elevate endogenous nocturnal melatonin levels in patients, which may contribute to both its somnolence side effect and its potential utility in sleep disturbance [46].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at registered doses are:

- Nausea (up to 40 percent at initiation, typically declining to 10 to 15 percent after 1 to 2 weeks of continued treatment; the most common cause of early discontinuation)
- Somnolence and drowsiness (22 to 27 percent)
- Insomnia (21 to 35 percent)
- Headache (22 to 35 percent)
- Asthenia (14 to 26 percent)
- Diarrhea (11 to 18 percent)
- Dry mouth (10 to 14 percent)
- Dizziness (11 to 15 percent)
- Anorexia (6 to 14 percent)
- Sexual dysfunction (incidence variable, estimated at 2 to 15 percent in clinical trials, likely underreported; includes decreased libido, anorgasmia, and ejaculatory delay)

These adverse-event rates are generally comparable to or slightly more favorable than the other SSRIs. Fluvoxamine is associated with less sexual dysfunction and less weight gain than paroxetine and sertraline in comparative analyses, but more nausea and somnolence than escitalopram and sertraline [39, 40].

11.2 Serious adverse events

Serotonin syndrome. A rare but potentially life-threatening condition characterized by mental status changes (agitation, confusion, delirium), autonomic instability (tachycardia, labile blood pressure, hyperthermia, diaphoresis), and neuromuscular abnormalities (clonus, hyperreflexia, tremor, rigidity). Risk is highest with concurrent serotonergic agents, particularly MAOIs, but can occur with fluvoxamine monotherapy at high doses or in overdose [47].

Suicidality. Fluvoxamine carries the SSRI class-wide boxed warning regarding increased risk of suicidal thinking and behavior in children, adolescents, and young adults (under 25 years) during early treatment. The risk is highest during the first 1 to 2 months of treatment or during dose changes. Close monitoring is required during these periods [12].

Bleeding. SSRIs including fluvoxamine impair platelet serotonin uptake and storage, reducing platelet aggregation and increasing bleeding time. The risk of gastrointestinal bleeding, epistaxis, ecchymosis, and postoperative bleeding is modestly increased, particularly in combination with NSAIDs, aspirin, or anticoagulants [48].

QT prolongation. Fluvoxamine has not been associated with clinically significant QT prolongation at therapeutic doses in the available data, distinguishing it from citalopram and escitalopram, which carry dose-dependent QT prolongation warnings. However, QT monitoring is advisable in patients receiving concurrent QT-prolonging medications.

Withdrawal syndrome. Abrupt discontinuation of fluvoxamine after prolonged use can produce a discontinuation syndrome characterized by dizziness, nausea, paresthesias, irritability, insomnia, and electric shock sensations. The severity is generally less than that reported with paroxetine and venlafaxine. Gradual dose tapering over 2 to 4 weeks is recommended.

Hepatotoxicity. Rare cases of hepatic enzyme elevation and clinically apparent hepatotoxicity have been reported. Routine hepatic monitoring is not required, but liver function should be assessed in patients developing jaundice or other signs of hepatic dysfunction.

11.3 Overdose

Fluvoxamine has a relatively favorable safety profile in overdose compared to tricyclic antidepressants. In reported overdose cases, symptoms include nausea, vomiting, diarrhea, somnolence, dizziness, tachycardia, bradycardia, and (at very high doses) seizures and cardiac conduction abnormalities. Fatal outcomes from fluvoxamine monotherapy overdose are rare. Treatment is supportive, with gastric lavage and activated charcoal if presentation is within 1 hour, and symptomatic management [49].

11.4 Pregnancy and lactation

Animal reproductive studies have demonstrated adverse developmental effects at maternally toxic doses. Epidemiological data from SSRI exposure during pregnancy suggest a small but statistically significant increase in the risk of persistent pulmonary hypertension of the newborn and neonatal adaptation syndrome (jitteriness, feeding difficulty, respiratory distress) with third-trimester exposure [31]. The compound is classified as FDA pregnancy category C. Decisions regarding use in pregnancy should balance the risk of untreated maternal psychiatric illness against the potential fetal risks. Fluvoxamine is excreted in breast milk at low concentrations, and breastfeeding is generally considered compatible under clinical supervision.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five serotonergic or sigma-1-active compounds against fluvoxamine, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five compounds were selected to represent the principal pharmacological alternatives to fluvoxamine across its core indications (OCD, depression, anxiety) and its distinguishing sigma-1 receptor mechanism.

12.1 Sertraline (Zoloft)

Mechanism: Selective serotonin reuptake inhibitor with moderate sigma-1 receptor affinity (K_i approximately 57 nM) and weak dopamine transporter inhibition [1, 24]. Sertraline is the SSRI with the second-highest sigma-1 receptor affinity after fluvoxamine.

Development trajectory and clinical state: Sertraline was developed by Pfizer, approved by the FDA in 1991 for MDD, and subsequently approved for OCD, panic disorder, PTSD, premenstrual dysphoric disorder, and social anxiety disorder. It is one of the most widely prescribed antidepressants worldwide, with an established safety database spanning more than three decades and billions of patient-days of exposure [50].

Novelty: Low. Sertraline is a conventional SSRI with well-characterized pharmacology. The sigma-1 receptor component is present but at approximately half the potency of fluvoxamine and has received substantially less research attention.

Effect size: In OCD, sertraline produces response rates of approximately 40 to 60 percent, broadly equivalent to fluvoxamine [15, 32]. In MDD, sertraline ranks among the more effective and better-tolerated SSRIs in network meta-analyses [39, 40]. In PTSD, sertraline is one of two FDA-approved SSRIs (with paroxetine) and has the strongest evidence base.

Promising potential: Moderate. Sertraline is a well-established, broadly indicated SSRI with no novel repositioning trajectory comparable to fluvoxamine's COVID-19 and anti-inflammatory applications. Its sigma-1 receptor activity has not been developed as a clinical differentiator.

Side-effect profile: Generally well tolerated. Higher rates of diarrhea than fluvoxamine; lower rates of somnolence. Comparable sexual dysfunction. Less potent CYP inhibition than fluvoxamine, producing a substantially lower drug-drug interaction burden (sertraline is a mild CYP2D6 inhibitor and does not significantly inhibit CYP1A2) [9].

Overall validation: High. The most extensively validated SSRI by breadth of approved indications, number of randomized controlled trials, and clinical experience.

Comparison to fluvoxamine: Sertraline has broader approved indications and a more favorable drug-drug interaction profile than fluvoxamine. Fluvoxamine has approximately 2-fold greater sigma-1 receptor potency, confirmed by PET imaging at therapeutic doses, and a uniquely developed anti-inflammatory and anti-infective repositioning trajectory. For OCD-specific applications, the two compounds are broadly equivalent in efficacy. For sigma-1-dependent research applications (anti-inflammatory, cytoprotective), fluvoxamine is the more appropriate pharmacological tool based on receptor potency and available translational data.

12.2 Escitalopram (Lexapro)

Mechanism: Selective serotonin reuptake inhibitor. The S-enantiomer of citalopram. The most SERT-selective compound among the marketed SSRIs, with negligible affinity for sigma-1 receptors (K_i greater than 1000 nM), norepinephrine and dopamine transporters, and monoamine receptors [24]. An allosteric binding site on the SERT may contribute to its high selectivity and apparent clinical advantage [51].

Development trajectory and clinical state: Developed by Lundbeck and Forest Laboratories. FDA-approved in 2002 for MDD and generalized anxiety disorder. Widely considered the best-tolerated SSRI on the basis of the Cipriani et al. (2009, 2018) network meta-analyses [39, 40].

Novelty: Low. Escitalopram is a refinement (single-enantiomer selection) of an existing SSRI rather than a mechanistically novel agent.

Effect size: In MDD, escitalopram is ranked among the most effective SSRIs, with a modest but consistent advantage over citalopram, fluoxetine, and fluvoxamine in network meta-analyses [39, 40]. In OCD, escitalopram demonstrates efficacy comparable to the other SSRIs at 10 to 20 mg daily [32]. In generalized anxiety disorder, escitalopram has strong placebo-controlled evidence.

Promising potential: Moderate. Escitalopram has no sigma-1 receptor activity and therefore no repositioning trajectory for anti-inflammatory or cytoprotective applications. Its clinical position is stable but mature.

Side-effect profile: The best-tolerated SSRI in most comparative analyses. Lower rates of nausea, somnolence, and sexual dysfunction than fluvoxamine, sertraline, and paroxetine. Dose-dependent QT prolongation has been identified, leading to a maximum recommended dose reduction to 20 mg daily [52]. Drug-drug interaction burden is minimal (weak CYP2D6 inhibition, negligible CYP1A2 and CYP3A4 effects).

Overall validation: High. Broadly validated as a first-line SSRI for MDD and anxiety disorders.

Comparison to fluvoxamine: Escitalopram is more effective (by a small margin) and better tolerated than fluvoxamine for MDD in network meta-analytic rankings. Fluvoxamine is differentiated by sigma-1 receptor agonism and the associated anti-inflammatory pharmacology, potent CYP1A2 inhibition (relevant for drug-drug interactions but also for melatonin potentiation), and a stronger evidence base in OCD relative to escitalopram. For pure antidepressant or anxiolytic applications where drug-drug interactions are a concern, escitalopram is generally preferred. For OCD or sigma-1-dependent research applications, fluvoxamine is the more appropriate choice.

12.3 Paroxetine (Paxil)

Mechanism: Selective serotonin reuptake inhibitor with the highest SERT affinity among the SSRIs (K_i approximately 0.13 nM), moderate norepinephrine transporter inhibition at higher doses, and weak muscarinic acetylcholine receptor antagonism [24]. Paroxetine has negligible sigma-1 receptor affinity (K_i greater than 1000 nM).

Development trajectory and clinical state: Developed by SmithKline Beecham (now GSK). FDA-approved in 1992 for MDD, subsequently approved for OCD, panic disorder, SAD, generalized anxiety disorder, and PTSD. Subject to significant con-

troversty regarding withdrawal syndrome severity and suicidality risk in adolescents, leading to regulatory action and litigation [53].

Novelty: Low. Conventional SSRI pharmacology with anticholinergic liability.

Effect size: Among the most effective SSRIs for OCD in some comparative analyses, possibly reflecting the contribution of high SERT potency and norepinephrine reuptake inhibition at higher doses [15, 32]. Broadly equivalent to other SSRIs in MDD. Strong evidence base in panic disorder and PTSD (one of two FDA-approved SSRIs for PTSD).

Promising potential: Low. Mature product with well-characterized limitations. No sigma-1 receptor activity and no repositioning trajectory.

Side-effect profile: Higher rates of weight gain, sexual dysfunction, and anticholinergic effects (dry mouth, constipation, sedation) than fluvoxamine and sertraline. Significantly more severe discontinuation syndrome than any other SSRI, attributable to the short half-life (approximately 21 hours) and potent SERT binding producing rapid rebound effects [53]. Drug-drug interaction profile: potent CYP2D6 inhibitor, moderate CYP3A4 inhibitor, but minimal CYP1A2 effect.

Overall validation: High for OCD and anxiety disorders. Reduced in clinical preference relative to the 1990s peak due to tolerability and withdrawal concerns.

Comparison to fluvoxamine: Paroxetine has higher SERT potency and broader approved indications (including PTSD). Fluvoxamine has sigma-1 receptor agonism, better tolerability for weight gain and sexual dysfunction, less severe discontinuation syndrome, and a unique anti-inflammatory repositioning profile. Fluvoxamine has a more problematic drug-drug interaction profile through CYP1A2 inhibition, while paroxetine has a more problematic profile through CYP2D6 inhibition. For OCD-specific applications, the two compounds are broadly equivalent. For research applications requiring sigma-1 receptor engagement, paroxetine is pharmacologically unsuitable.

12.4 Clomipramine (Anafranil)

Mechanism: Tricyclic antidepressant with potent, nonselective serotonin and norepinephrine reuptake inhibition, moderate sigma-1 receptor affinity (K_i approximately 280 nM), significant antagonism at muscarinic, histaminergic (H1), and al-

pha-1 adrenergic receptors [24, 54]. The principal active metabolite, desmethyl-clomipramine, is a potent norepinephrine reuptake inhibitor.

Development trajectory and clinical state: Developed by Geigy (now Novartis). FDA-approved in 1989 for OCD, the first medication specifically approved for this indication. Registered for depression in most other jurisdictions. Clomipramine was the historical gold standard for OCD pharmacotherapy before the SSRIs and remains a second-line agent for SSRI-refractory OCD [54].

Novelty: Low. Classic tricyclic pharmacology with broad receptor binding.

Effect size: In OCD, clomipramine produces the largest effect sizes of any single serotonergic agent in some meta-analyses, though this advantage may reflect methodological differences in the older trial designs rather than true pharmacological superiority [15, 32]. In MDD, clomipramine is a highly effective antidepressant, broadly comparable to or slightly more effective than the SSRIs, at the cost of substantially greater adverse-event burden.

Promising potential: Low. Mature product with well-characterized limitations. The broad receptor binding profile limits its utility for sigma-1-specific or anti-inflammatory research.

Side-effect profile: Substantially more adverse events than fluvoxamine and the SSRIs: anticholinergic effects (dry mouth 84 percent, constipation 47 percent, urinary retention), sedation, orthostatic hypotension, weight gain (approximately 18 percent of patients gain more than 7 percent body weight), sexual dysfunction (approximately 40 to 80 percent), and seizure risk (approximately 0.5 to 2 percent at doses above 250 mg daily) [54]. Overdose toxicity is significantly greater than fluvoxamine (cardiac conduction abnormalities, seizures, death).

Overall validation: High for OCD, particularly SSRI-refractory OCD. Well validated for depression. Limited by tolerability.

Comparison to fluvoxamine: Clomipramine may have marginally greater OCD efficacy than fluvoxamine but with a substantially worse tolerability profile. Fluvoxamine is preferred as first-line OCD treatment on the basis of the risk-benefit ratio; clomipramine is reserved for SSRI-refractory cases or augmentation strategies. For sigma-1-dependent research, clomipramine is unsuitable due to its approximately 8-fold lower sigma-1 affinity relative to fluvoxamine and its confound-

ing broad receptor binding at muscarinic, histaminergic, and adrenergic receptors. For anti-inflammatory research, clomipramine's multiple non-serotonergic receptor interactions make mechanistic attribution problematic.

12.5 Vortioxetine (Trintellix)

Mechanism: Multimodal serotonergic agent. Serotonin reuptake inhibitor (K_i approximately 1.6 nM at SERT), 5-HT₃ receptor antagonist, 5-HT₇ receptor antagonist, 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, and 5-HT_{1A} receptor agonist [55]. Vortioxetine does not have characterized sigma-1 receptor activity.

Development trajectory and clinical state: Developed by Lundbeck and Takeda. FDA-approved in 2013 for MDD. The compound is positioned as a cognitive-enhancing antidepressant on the basis of its multimodal serotonergic pharmacology and clinical data demonstrating improvements on cognitive testing batteries (DSST, processing speed) independent of mood improvement [55, 56].

Novelty: Moderate to high. The multimodal serotonergic mechanism is pharmacologically distinct from the SSRIs and from fluvoxamine's SSRI-plus-sigma-1 profile.

Effect size: In MDD, vortioxetine produces effect sizes broadly comparable to the SSRIs and SNRIs, with a differentiated cognitive improvement signal at 10 to 20 mg daily [55, 56]. Evidence in OCD is limited; the compound is not approved for this indication.

Promising potential: Moderate. The cognitive improvement differentiation is a unique positioning in the antidepressant market. No anti-inflammatory or anti-infective repositioning trajectory comparable to fluvoxamine.

Side-effect profile: Nausea is the principal adverse event (dose-dependent, up to 32 percent at 20 mg). Lower rates of sexual dysfunction than the SSRIs. No significant CYP inhibition, producing a minimal drug-drug interaction burden [55]. Weight neutrality.

Overall validation: Moderate. Approved only for MDD. The cognitive enhancement data from the FOCUS and CONNECT trials are novel and represent a genuine pharmacological differentiation, though the compound lacks the breadth of indication and depth of clinical experience of the SSRIs [56].

Comparison to fluvoxamine: Vortioxetine and fluvoxamine represent two different approaches to extending antidepressant pharmacology beyond SERT inhibition. Vortioxetine adds multimodal serotonergic receptor activity targeting cognitive function; fluvoxamine adds sigma-1 receptor agonism targeting cytoprotection and anti-inflammatory activity. For MDD with cognitive symptoms, vortioxetine may be preferred. For OCD, fluvoxamine has substantially stronger evidence. For sigma-1-dependent research, vortioxetine is pharmacologically inappropriate. The two compounds are complementary research tools for understanding different dimensions of serotonergic and non-serotonergic contributions to antidepressant efficacy.

12.6 Comparator summary

The five compounds occupy distinct positions in the serotonergic pharmacology space. **Sertraline** is the most broadly validated SSRI with moderate sigma-1 receptor affinity but without a developed sigma-1 research trajectory. **Escitalopram** is the most SERT-selective and best-tolerated SSRI but lacks sigma-1 receptor activity entirely. **Paroxetine** has the highest SERT potency and broad anxiolytic indications but is limited by tolerability concerns and absent sigma-1 receptor activity. **Clomipramine** has the historically strongest OCD efficacy signal but is limited by extensive adverse events and broad non-selective receptor binding. **Vortioxetine** represents a novel multimodal approach with cognitive differentiation but lacks OCD evidence and sigma-1 receptor activity.

Fluvoxamine occupies a unique position in this comparator landscape: it is the only compound with potent, PET-confirmed sigma-1 receptor agonism at therapeutic doses, the only SSRI with positive randomized trial evidence for a non-psychiatric indication (COVID-19), and the compound with the most developed anti-inflammatory and cytoprotective repositioning trajectory among the SSRIs. Its principal limitations relative to the comparators are a more problematic drug-drug interaction profile (potent CYP1A2 inhibition), a slightly lower tolerability ranking in network meta-analyses (more nausea and somnolence than escitalopram and sertraline), and the absence of FDA approval for MDD (limiting its regulatory positioning in the United States).

The principal practical question for the research-clinical positioning of fluvoxamine is whether the sigma-1 receptor agonism constitutes a clinically meaningful differentiator or an incidental pharmacological feature. The COVID-19 data from

the TOGETHER trial provide the strongest evidence to date that the sigma-1 receptor activity translates to clinical benefit in an inflammatory condition, and the pre-clinical anti-inflammatory literature (ER stress modulation, NLRP3 inhibition, acute lung injury attenuation) provides a coherent mechanistic framework. The compound's continued utility as both a clinical SSRI and a sigma-1 receptor pharmacological tool positions it uniquely among the serotonergic antidepressants for translational research applications spanning psychiatry, inflammation, and infectious disease.

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