

RESEARCH MONOGRAPH . COMPOUND PROFILE

2-Bromo-LSD

A brominated lysergic acid diethylamide derivative originally synthesized by Hofmann and Troxler in 1957, distinguished from the parent compound LSD by non-hallucinogenic biased partial agonism at the serotonin 5-HT_{2A} receptor, antagonism at the cardiotoxicity-associated 5-HT_{2B} receptor, potent 5-HT₁ pan-agonism, and emerging therapeutic interest in cluster headache prophylaxis and rapid-acting antidepressant development.

DOCUMENT	KDC-MN-1571
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Non-hallucinogenic lysergamide serotonin receptor modulator with biased 5-HT _{2A} partial agonism and 5-HT ₁ pan-agonism

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ABSTRACT

2-Bromo-lysergic acid diethylamide (2-Br-LSD; BOL-148; CAS 478-84-2), the 2-bromo derivative of lysergic acid diethylamide (LSD), is a non-hallucinogenic lysergamide serotonin receptor modulator first synthesized by Franz Troxler and Albert Hofmann at Sandoz in 1957 as part of a systematic structure-activity exploration of ergoline pharmacology. The compound binds with high affinity to the same serotonin, dopamine, and adrenergic receptor targets as LSD but exhibits a fundamentally different functional profile: at the serotonin 5-HT_{2A} receptor, 2-Br-LSD acts as a biased partial agonist with an E_{max} of approximately 60 percent of the serotonin reference response (compared to approximately 92 percent for LSD), weak beta-arrestin recruitment (E_{max} approximately 37 percent), and no induction of the head-twitch response in mice across a 100-fold dose range, the accepted rodent behavioral proxy for human hallucinogenic activity. At the serotonin 5-HT_{2B} receptor, 2-Br-LSD acts as an antagonist, eliminating the cardiac valvulopathy liability that constrains chronic dosing of LSD and other ergoline agonists at this target. Across the 5-HT₁ receptor family (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), the compound demonstrates potent pan-agonism, engaging the established anti-migraine drug targets 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} at sub-nanomolar to low-nanomolar functional concentrations.

The therapeutic interest in 2-Br-LSD spans two principal domains. The first is cluster headache prophylaxis, supported by a 2010 open-label case series (Karst, Halpern, Bernateck, Passie) in which five patients with chronic or episodic cluster headache received

three oral doses of 2-Br-LSD (approximately 30 micrograms per kilogram) over 10 days and experienced pronounced reductions in attack frequency, including sustained remissions of one to nine months. The second is rapid-acting antidepressant activity, supported by the Lewis et al. (2023) characterization in Cell Reports demonstrating that 2-Br-LSD promotes dendritogenesis and spinogenesis in primary rat cortical neurons at 1 to 10 micromolar concentrations (comparable to ketamine), reverses chronic variable stress-induced behavioral deficits in mice with effects persisting at least 28 days after a four-dose regimen, and does so through a 5-HT_{2A}-dependent mechanism confirmed by volinanserin blockade both in vitro and in vivo. The compound does not produce tolerance on seven-day repeated dosing, in contrast to classical psychedelics that produce rapid tachyphylaxis.

Multiple pharmaceutical development programs are active. BetterLife Pharma is advancing BETR-001 (2-Br-LSD) through IND-enabling studies for major depressive disorder and cluster headache, with FDA pre-IND feedback received in January 2022 confirming suitability of the development program for IND filing. Seaport Therapeutics is developing SPT-348 (Glyph2BLSD), an oral prodrug of 2-Br-LSD, for treatment-resistant depression and post-traumatic stress disorder, with first-in-human-enabling studies underway. Cryo-electron microscopy structures of the 5-HT_{2A} receptor bound to 2-Br-LSD in complex with mini-Gq protein (PDB 9AS0; Gumpfer, Fay, Roth) have elucidated the structural basis of its biased partial agonism and provide a molecular template for next-generation non-hallucinogenic psychoplastogen design.

Pharmacokinetics in mice demonstrate rapid absorption (T_{max} 0.2 hours in plasma, 0.17 hours in brain), brain penetrance (brain-to-plasma ratio 0.27 to 0.75), and short central nervous system residence (brain half-life 0.7 to 1.3 hours, below detection at 4 hours). Human pharmacokinetic data are limited to the Karst et al. (2010) cluster headache case series, in which oral doses of approximately 2 to 3 milligrams produced mild, transient subjective effects lasting 1 to 2 hours without hallucinogenic phenomena. The compound is not scheduled in the United States, Canada, Germany, or the European Union. This monograph reviews the chemistry and synthesis; the comprehensive multi-receptor pharmacology across 33 aminergic GPCRs; the preclinical neuroplasticity, behavioral, and cardiovascular safety data; the clinical evidence in cluster headache; the active pharmaceutical development programs; sourcing, reconstitution, and handling considerations; stack interactions; adverse-event signal; and a comparative assessment of five lysergamide and serotonergic compounds against 2-Br-LSD on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Not assigned. The compound has not received an INN designation; regulatory and scientific literature use the chemical name or development codes.

Common names: 2-Bromo-LSD, 2-Br-LSD, bromolysergide, bromo-LSD.

Development and laboratory codes: BOL-148 (Sandoz, original designation by Hofmann and Troxler), BETR-001 (BetterLife Pharma), TD-0148A (BetterLife Pharma, earlier designation), NYPRG-101 (New York Headache Center), SPT-348 / Glyph2BLSD (Seaport Therapeutics, prodrug form).

Chemical Abstracts Service registry number: 478-84-2 (free base).

International Union of Pure and Applied Chemistry name: (6aR,9R)-5-bromo-N,N-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide.

PubChem CID: 164593.

1.2 Structural class and chemistry

2-Bromo-LSD is a brominated ergoline derivative of the lysergamide structural class. It is produced by electrophilic aromatic substitution (bromination) at the 2-position (also designated the 5-position on the indole ring in some numbering conventions) of the tetracyclic ergoline core of lysergic acid diethylamide. The bromine atom at this position is the sole structural modification relative to LSD and is responsible for the dramatic shift in functional pharmacology from near-full agonism to biased partial agonism at the 5-HT_{2A} receptor.

Molecular formula: C₂₀H₂₄BrN₃O (free base).

Exact mass: 401.1103 g/mol (monoisotopic, free base).

Molecular weight: 402.34 g/mol (free base).

Physical properties: Crystalline solid. Soluble in dimethyl sulfoxide, methanol, and aqueous buffers at pharmacologically relevant concentrations. The compound shares the general physicochemical properties of the lysergamide class, including moderate lipophilicity sufficient for blood-brain barrier penetration and photosensitivity requiring light-protected storage.

Stereochemistry: 2-Bromo-LSD retains the (6aR,9R) absolute configuration of the parent compound LSD. Both stereocenters (C-6a and C-9) are essential for serotonin receptor binding; the (6aR,9R) configuration corresponds to the pharmacologically active (+)-lysergic acid series. The 2-bromo substitution does not introduce additional stereocenters. Investigators acquiring research-grade material should confirm the correct stereochemistry, as the inactive iso-lysergic acid series [(6aR,9S) configuration] can be present as a synthetic impurity.

1.3 Synthesis

The original synthesis of 2-Bromo-LSD was reported by Troxler and Hofmann in 1957 [1]. The classical method involves direct bromination of LSD using N-bromosuccinimide (NBS) in dioxane. In the original procedure, 25 grams of LSD in 1.2 liters of dioxane was treated with 13.2 grams of NBS in 400 milliliters of dioxane, yielding 11 grams of crude product that was purified by recrystallization. The yield was moderate, and the reaction required careful exclusion of light and moisture to prevent degradation of the photosensitive ergoline nucleus.

Alternative synthesis routes have been developed and patented. The BetterLife Pharma patent (US 2016/0237080 A1) describes a route proceeding from methylergometrine (methylergonovine), which is brominated with NBS to produce an intermediate bromo-lysergic acid derivative, followed by base-mediated hydrolysis to bromo-lysergic acid, and subsequent acylation with diethylamine using a suitable coupling agent to yield 2-Br-LSD [2]. This route avoids the use of LSD as a starting material, which carries regulatory scheduling implications in most jurisdictions, and instead begins from the unscheduled ergot alkaloid methylergometrine.

Radioactive synthesis using elemental bromine (with tritium or carbon-14 labeling) has been employed for receptor binding studies, with reported yields of 5 to 15 percent [3]. The lower yield in the radioactive synthesis reflects the more aggressive bromination conditions required for isotope incorporation.

Purification is accomplished by column chromatography or preparative high-performance liquid chromatography, followed by recrystallization from appropriate solvent systems. The compound is characterized by nuclear magnetic resonance spectroscopy (the 2-bromo substitution is confirmed by the absence of the H-2 aromatic proton signal and by characteristic downfield shifts in adjacent ring protons), mass spectrometry (the bromine isotope pattern at M and M+2 is diagnostic), and high-performance liquid chromatography.

2. Abstract

2-Bromo-lysergic acid diethylamide (2-Br-LSD; BOL-148) is a non-hallucinogenic lysergamide that binds with high affinity to the serotonin 5-HT_{2A} receptor, the principal pharmacological target of classical psychedelics, but acts as a biased partial agonist with an E_{max} of approximately 60 percent (compared to approximately 92 percent for LSD) and weak beta-arrestin recruitment (E_{max} approximately 37 percent), producing no head-twitch response in mice and no hallucinogenic effects in humans at moderate to high doses [4, 5]. The compound was first synthesized by Troxler and Hofmann at Sandoz in 1957 [1] and was initially characterized as a serotonin antagonist capable of blocking the psychedelic effects of LSD in human subjects [6].

Contemporary receptor profiling across 33 aminergic G protein-coupled receptors has revealed a pharmacological profile more complex than the early antagonist characterization suggested. 2-Br-LSD demonstrates potent pan-agonism at all five 5-HT₁ receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), engaging the clinically validated anti-migraine targets 5-HT_{1B}/1D/1F at sub-nanomolar to low-nanomolar concentrations [4]. It acts as an antagonist at the 5-HT_{2B} receptor, eliminating the cardiac valvulopathy risk associated with chronic serotonin 5-HT_{2B} agonism [4]. It demonstrates sub-nanomolar partial agonism at the 5-HT₆ receptor (EC₅₀ 0.35 nM) and antagonism or inverse agonism at the 5-HT_{5A} and 5-HT₇ receptors [4]. At dopamine receptors, the compound shows activity at D₂ and D₄ within its top 10 targets (EC₅₀ values 0.35 to 1.2 nM) [4].

The compound promotes structural neuroplasticity (dendritogenesis and spinogenesis) in primary cortical neurons at 1 to 10 micromolar concentrations through a 5-HT_{2A}-dependent mechanism, produces antidepressant-like behavioral effects in stressed and stress-naïve mice, and does not induce tolerance on repeated dosing [4]. An open-label clinical case series demonstrated efficacy in cluster headache prophylaxis, with sustained remissions of one to nine months after a three-dose oral regimen [5]. Multiple pharmaceutical development programs (BetterLife Pharma BETR-001; Seaport Therapeutics SPT-348) are advancing the compound toward human clinical trials for major depressive disorder, treatment-resistant depression, post-traumatic stress disorder, and cluster headache.

3. Discovery and Development History

3.1 Origin

2-Bromo-LSD was synthesized by Franz Troxler and Albert Hofmann at the Sandoz Forschungsinstitut (Basel, Switzerland) in 1957 as part of a systematic program to explore the structure-activity relationships of ergoline derivatives [1]. Hofmann, who had discovered the psychoactive properties of LSD in 1943, was interested in dissecting the relationship between ergoline structure and hallucinogenic activity. The bromination of LSD at the 2-position of the indole ring was one of several modifications explored; others included hydrogenation of the D-ring double bond, N-methylation, and various ring substitutions. The 2-bromo derivative was notable for retaining high-affinity serotonin receptor binding while lacking hallucinogenic activity in animal behavioral assays and in early human studies.

3.2 Early pharmacological characterization

In the 1950s and 1960s, 2-Br-LSD (designated BOL-148 by Sandoz) was characterized principally as a serotonin antagonist. Studies demonstrated that BOL-148 could block the psychedelic effects of subsequently administered LSD in some (though not all) human subjects, consistent with competitive antagonism at serotonin receptors [6]. The compound became a standard pharmacological tool for dissecting serotonin receptor subtypes in the pre-molecular-cloning era, used alongside methysergide and cyproheptadine in receptor classification studies.

The Burris and Sanders-Bush (1992) study at Vanderbilt formally characterized the binding kinetics of bromo-lysergic acid diethylamide at 5-HT₂ receptors in rat brain, demonstrating that both LSD and BOL produced unsurmountable antagonism (blockade that could not be overcome by increasing serotonin concentration) attributable to slowly reversible receptor occupancy rather than allosteric modulation [7]. The off-rate of tritiated LSD from the 5-HT₂ receptor was approximately 20 minutes, compared to approximately 4 minutes for ketanserin, and BOL showed similarly slow dissociation kinetics. This study established that 2-Br-LSD occupied the same orthosteric binding site as LSD but with different functional consequences.

3.3 Cluster headache discovery

The therapeutic potential of 2-Br-LSD in cluster headache emerged from anecdotal reports by cluster headache patients who had self-treated with LSD or psilocybin and observed sustained reductions in attack frequency [8]. The observation that the non-hallucinogenic analogue BOL-148 might produce similar prophylactic effects without psychedelic liability prompted the Karst, Halpern, Bernateck, and Passie (2010) open-label case series, which provided the first formal clinical evidence for this indication [5]. The study demonstrated sustained cluster period termination and attack frequency reduction in 5 patients treated with three oral doses over 10 days, establishing a clinical rationale for further investigation.

3.4 Contemporary molecular pharmacology

The Lewis et al. (2023) publication in Cell Reports, conducted in collaboration with BetterLife Pharma, provided the first comprehensive multi-receptor profiling of 2-Br-LSD across 33 aminergic GPCRs and characterized its psychoplastogenic and antidepressant-like properties [4]. This study reframed 2-Br-LSD from a simple serotonin antagonist to a complex multi-target ligand with biased signaling properties at the 5-HT_{2A} receptor and therapeutic mechanisms distinct from both classical psychedelics and conventional antidepressants.

3.5 Structural biology

Cryo-electron microscopy structures of the 5-HT_{2A} receptor bound to 2-Br-LSD in complex with mini-Gq protein and scFv16 (PDB ID: 9AS0) were solved by Gumpfer, Fay, and Roth and deposited in the Protein Data Bank [9]. These structures, part of a broader campaign resolving seven cryo-EM structures of hallucinogenic and non-hallucinogenic compounds bound to the 5-HT_{2A} receptor, revealed the molecular basis for the biased partial agonism of 2-Br-LSD: the bulky bromine substituent at the 2-position sterically constrains receptor activation, limiting the conformational shift required for full G protein coupling and beta-arrestin recruitment while still permitting partial activation sufficient for the psychoplastogenic signaling cascade.

3.6 Active pharmaceutical development

BetterLife Pharma (Vancouver, Canada) designated 2-Br-LSD as BETR-001 and received FDA pre-IND feedback in January 2022 confirming the suitability of the development plan for an IND filing targeting major depressive disorder [10]. The company has conducted IND-enabling studies including GMP manufacturing, formulation development, and non-clinical safety pharmacology. As of the most recent public disclosures (2024), the compound remains in IND-enabling development.

Seaport Therapeutics (Boston, Massachusetts) is developing SPT-348 (Glyph2BLSD), an oral prodrug of 2-Br-LSD designed to improve oral bioavailability and provide sustained plasma concentrations [11]. The prodrug is in first-in-human-enabling studies for treatment-resistant depression and post-traumatic stress disorder. Seaport raised \$254.9 million in a Nasdaq IPO to support its pipeline of oral psychiatric therapies, of which SPT-348 is a preclinical-stage candidate.

4. Mechanism of Action

2-Bromo-LSD is a multi-target serotonergic ligand with a complex pharmacological profile spanning serotonin, dopamine, and adrenergic receptor families. Its principal pharmacological activities, characterized across 33 aminergic GPCRs in the Lewis et al. (2023) comprehensive profiling study [4], distinguish it from both the parent compound LSD and from conventional serotonin antagonists.

4.1 Serotonin 5-HT_{2A} receptor biased partial agonism

The 5-HT_{2A} receptor is the principal pharmacological target of classical psychedelics (LSD, psilocybin, DMT, mescaline) and the receptor most strongly implicated in both hallucinogenic activity and psychoplastogenic neuroplasticity. 2-Br-LSD binds the 5-HT_{2A} receptor with sub-nanomolar affinity (EC₅₀ 0.81 nM in Gq-mediated calcium flux assays) but achieves only partial activation, with an E_{max} of approximately 59.8 percent of the serotonin reference response [4]. By comparison, LSD achieves an E_{max} of approximately 91.5 percent at the same receptor in the same assay system.

The biased signaling profile is evident in beta-arrestin recruitment: 2-Br-LSD produces weak beta-arrestin2 recruitment at the 5-HT_{2A} receptor (E_{max} approximately 36.9 percent), in contrast to the robust recruitment produced by LSD and other hallucinogenic 5-HT_{2A} agonists [4]. This G protein bias (preferential activation of Gq signaling relative to beta-arrestin recruitment) is hypothesized to underlie the dissociation between psychoplastogenic activity (which proceeds through Gq-mediated signaling cascades) and hallucinogenic activity (which may require beta-arrestin-dependent receptor internalization and sustained signaling from endosomal compartments, though this mechanistic model remains under active investigation).

The head-twitch response (HTR) in mice, the standard behavioral proxy for human hallucinogenic activity, is not induced by 2-Br-LSD across a 100-fold dose range (0.1 to 10 mg/kg), despite confirmed brain penetrance at these doses [4]. Pre-treatment with 2-Br-LSD dose-dependently attenuated DOI-induced HTR (76 percent blockade at 3 mg/kg), confirming 5-HT_{2A} receptor occupancy and functional antagonism of full agonist-induced hallucinogenic-like behavior. Neither 5-HT_{1A} antago-

nism (WAY-100,635) nor D2/D3 antagonism (raclopride) restored HTR in 2-Br-LSD-treated animals, ruling out masking of hallucinogenic activity by concurrent receptor interactions.

The structural basis for the biased partial agonism was elucidated by cryo-EM. The 2-bromo substituent occupies space within the orthosteric binding pocket of the 5-HT_{2A} receptor that constrains the receptor transmembrane domain rearrangement required for full G protein coupling, resulting in a partially activated receptor conformation that engages G_q sufficiently for downstream neuroplasticity signaling but insufficiently for the full activation pattern associated with hallucinogenic perception [9].

4.2 Serotonin 5-HT_{2B} receptor antagonism

At the 5-HT_{2B} receptor, 2-Br-LSD acts as an antagonist with no detectable agonist activity [4]. This is a critical pharmacological distinction from LSD, which is a potent 5-HT_{2B} agonist. Chronic 5-HT_{2B} agonism is the established mechanism of drug-induced cardiac valvulopathy, the adverse effect that led to the withdrawal of fenfluramine and pergolide and that constrains the chronic dosing of ergoline-derived medications. The 5-HT_{2B} antagonism of 2-Br-LSD eliminates this liability and permits consideration of chronic or repeated dosing regimens that would be contraindicated for LSD and other 5-HT_{2B} agonists.

4.3 Serotonin 5-HT₁ receptor pan-agonism

All five 5-HT₁ receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}) are within the top 10 targets of 2-Br-LSD by potency [4]. The compound demonstrates potent Gi/Go-coupled agonism across the entire 5-HT₁ family, including the three clinically validated anti-migraine drug targets: 5-HT_{1B} (the target of sumatriptan and other triptans), 5-HT_{1D} (engaged by sumatriptan and naratriptan), and 5-HT_{1F} (the target of lasmiditan). This 5-HT₁ pan-agonism provides a plausible mechanistic basis for the cluster headache prophylactic activity observed in the Karst et al. (2010) case series and is consistent with the broader observation that multiple ergoline and tryptamine compounds with 5-HT₁ agonist activity (LSD, psilocybin, methysergide) have been reported to produce sustained cluster headache remissions.

4.4 Activity at other serotonin receptor subtypes

At the 5-HT_{2C} receptor, 2-Br-LSD is a weak partial agonist (E_{max} approximately 45.8 percent), with reduced efficacy compared to LSD [4]. At the 5-HT_{5A} receptor, the compound acts as a potent antagonist (K_B 4.14 nM) [4]. At the 5-HT₆ receptor, sub-nanomolar partial agonism is observed (EC₅₀ 0.35 nM) [4]. At the 5-HT₇ receptor, the compound acts as an antagonist or inverse agonist [4]. The functional significance of these activities in the context of the therapeutic applications under investigation (mood disorders, cluster headache) is not fully characterized but may contribute to the overall pharmacological profile.

4.5 Dopamine and adrenergic receptor activity

The D₂ and D₄ dopamine receptors are within the top 10 targets of 2-Br-LSD (EC₅₀ values 0.35 to 1.2 nM) [4]. The compound is a weaker partial agonist at D₃ than LSD and lacks the strong D₁/D₅ agonism of the parent compound. At adrenergic receptors, 2-Br-LSD demonstrates antagonism at alpha-1A, alpha-1B, beta-1, and beta-2 subtypes, with mixed effects at alpha-2 subtypes [4]. The dopamine D₂ activity is relevant to the compound's potential psychiatric applications, though at the partial agonist efficacy observed, the D₂ contribution is likely modulatory rather than dominant.

4.6 Psychoplastogenic mechanism

2-Br-LSD promotes structural neuroplasticity in primary rat cortical neurons through a 5-HT_{2A}-dependent mechanism [4]. In dendritogenesis assays, 2-Br-LSD at 1 to 10 micromolar concentrations produced dose-dependent increases in Sholl crossing number and total dendritic length, with maximal effects comparable to ketamine (10 micromolar). In spinogenesis assays, 2-Br-LSD at 1 to 10 micromolar concentrations increased dendritic spine density at 24 hours post-treatment, again with effects at 10 micromolar comparable to ketamine [4].

The 5-HT_{2A} dependence of both effects was confirmed by volinanserin (M100,907), a selective 5-HT_{2A} antagonist: volinanserin at 0.1 to 1 micromolar completely blocked 2-Br-LSD-induced dendritogenesis and dendritic length increases in vitro [4]. In vivo, volinanserin (0.125 mg/kg) blocked the antidepressant-like effects of 2-Br-LSD in the forced swim test in both sexes [4]. The psychoplastogenic mechanism therefore proceeds through 5-HT_{2A}-mediated G_q signaling to downstream

neuroplasticity cascades, consistent with the broader psychoplastogen literature in which 5-HT_{2A} activation drives structural and functional synaptic remodeling through BDNF-TrkB, mTOR, and AMPA receptor-dependent pathways.

No cellular toxicity was detected at the concentrations producing maximal neuroplasticity effects [4], supporting the therapeutic window for psychoplastogenic activity without neurotoxicity.

5. Pharmacokinetics and Routes of Administration

5.1 Preclinical pharmacokinetics (mouse)

The pharmacokinetics of 2-Br-LSD have been characterized in mice following intraperitoneal administration [4]. Key parameters include:

Absorption and distribution: The compound is rapidly absorbed, with time to maximum plasma concentration (Tmax) of 0.2 hours. Brain Tmax is 0.17 hours, indicating rapid central nervous system penetration. The brain-to-plasma concentration ratio ranges from 0.27 to 0.75, confirming blood-brain barrier penetrance sufficient for central pharmacological effects [4].

Plasma concentrations: Maximum plasma concentrations are dose-dependent and sex-dependent, with males exhibiting 2- to 5-fold higher Cmax values than females at equivalent doses [4]. The basis for the sex difference has not been characterized but may reflect differences in body composition, hepatic metabolism, or plasma protein binding.

Elimination: The plasma half-life ranges from 0.9 to 2.6 hours (females) and 1.2 to 1.4 hours (males). Brain concentrations decline more rapidly, with a brain half-life of 0.7 to 1.3 hours, falling below the limit of detection at 4 hours post-administration [4]. The short central nervous system residence time, combined with the sustained behavioral and neuroplastic effects observed at 24 hours and beyond, suggests that the pharmacodynamic duration substantially exceeds the pharmacokinetic residence, consistent with a neuroplasticity-dependent mechanism that is triggered by receptor activation but sustained by downstream structural synaptic remodeling.

5.2 Human pharmacokinetic observations

Formal human pharmacokinetic studies with defined parameters (AUC, Cmax, clearance, volume of distribution, protein binding) have not been published for 2-Br-LSD. The available human exposure data derive from the Karst et al. (2010) cluster headache case series, in which five patients received oral doses of approxi-

mately 30 micrograms per kilogram body weight (total doses of 2.0 to 3.1 milligrams per administration) on three occasions over 10 days [5]. Subjective effects (mild "flabby feeling," "light drunk" sensation, "funny" feeling) were reported as lasting 1 to 2 hours after oral dosing, consistent with the short half-life observed in preclinical studies. No hallucinogenic effects, visual disturbances, or psychotic symptoms were observed at these doses.

Earlier human studies from the 1950s and 1960s, conducted as part of the original Sandoz pharmacological characterization, administered BOL-148 at various doses to healthy volunteers and psychiatric patients. These studies generally reported the absence of hallucinogenic effects at moderate to high doses, though isolated incidents of hallucinogenic-like responses were documented at very high doses. Formal pharmacokinetic parameters were not measured in these early studies.

5.3 Routes of administration

The principal route of administration in both preclinical research and the clinical case series is oral. The compound is absorbed from the gastrointestinal tract with sufficient bioavailability to produce central pharmacological effects at the doses studied. Intraperitoneal administration is the standard preclinical route for mouse behavioral studies [4]. Subcutaneous and intravenous administration have been used in early pharmacological studies but are not the routes under current clinical development.

The Seaport Therapeutics prodrug SPT-348 (Glyph2BLSD) is designed as an oral formulation with modified release characteristics intended to improve the pharmacokinetic profile of the parent compound for chronic or repeated dosing in psychiatric indications [11].

5.4 Metabolism

The metabolic pathways of 2-Br-LSD in humans have not been formally characterized. By structural analogy with LSD, the compound is expected to undergo hepatic oxidative metabolism, principally through cytochrome P450 enzymes (CYP3A4 is the dominant isoform for LSD N-demethylation and hydroxylation). The bromine substituent may alter the metabolic profile relative to LSD by blocking electrophilic aromatic substitution at the 2-position and potentially redirecting metabolism to

other ring positions or to the diethylamide side chain. Glucuronidation of hydroxylated metabolites and renal excretion of conjugates are expected to constitute the principal elimination pathway by analogy with LSD metabolism.

Investigators conducting pharmacokinetic studies should note the potential for CYP3A4-mediated drug interactions, particularly with strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) and inducers (rifampin, carbamazepine, phenytoin, St. John's wort), although these interactions have not been formally characterized for 2-Br-LSD.

6. Preclinical Pharmacology

6.1 Head-twitch response studies

The head-twitch response (HTR) in mice is the validated behavioral proxy for human hallucinogenic activity of 5-HT_{2A} receptor agonists. 2-Br-LSD does not induce HTR across a 100-fold dose range (0.1 to 10 mg/kg, intraperitoneal) in C57BL/6J mice, despite confirmed brain penetrance at these doses [4]. By comparison, LSD at 0.1 mg/kg produced significant HTR in the same experimental system.

Pre-treatment with 2-Br-LSD dose-dependently attenuated DOI-induced HTR: 3 mg/kg 2-Br-LSD reduced DOI-induced HTR by 76 percent [4]. This confirms that 2-Br-LSD occupies 5-HT_{2A} receptors in vivo at sufficient levels to block the effects of a full agonist, establishing the compound as a functional 5-HT_{2A} partial agonist/antagonist in the behavioral context of hallucinogenic-like activity.

Mechanistic dissection studies demonstrated that neither 5-HT_{1A} antagonism (WAY-100,635) nor D₂/D₃ antagonism (raclopride) restored HTR in 2-Br-LSD-treated mice, ruling out the hypothesis that concurrent 5-HT_{1A} or dopaminergic activity was masking an intrinsic hallucinogenic effect [4].

6.2 Tolerance studies

Seven-day repeated dosing of 2-Br-LSD (3 mg/kg/day, intraperitoneal) did not produce tolerance as measured by HTR challenge with DOI on day 8 [4]. In contrast, seven-day repeated dosing with DOI (a reference 5-HT_{2A} full agonist) produced significant tachyphylaxis ($p < 0.001$ versus vehicle control). The absence of tolerance with 2-Br-LSD is consistent with its biased partial agonist profile: the limited beta-arrestin recruitment and the partial receptor activation may be insufficient to drive the receptor downregulation and desensitization that underlie classical psychedelic tolerance (tachyphylaxis). This finding has practical implications for repeated dosing regimens in therapeutic applications, where tolerance to the antidepressant or headache-prophylactic effect would limit clinical utility.

6.3 Antidepressant-like behavioral effects

Stress-naïve mice (single dose, 24-hour pre-test): In the forced swim test (FST), 2-Br-LSD at 1 mg/kg (females) and 0.3 to 3 mg/kg (males) produced significant reductions in immobility time at 24 hours post-administration, consistent with antidepressant-like activity [4]. In the open field test (OFT), 2-Br-LSD at 1 to 3 mg/kg increased center exploration time in females without affecting total locomotion, consistent with anxiolytic-like activity rather than generalized hyperlocomotion [4].

Chronic variable stress (CVS) model in female mice: A four-dose regimen of 2-Br-LSD (1 mg/kg every 48 hours) fully restored center exploration in the OFT and partially reversed grooming deficits in the splash test in CVS-exposed mice [4]. A single acute dose of 3 mg/kg produced partial behavioral reversal. The four-dose regimen effects persisted at 28 days post-treatment, indicating sustained antidepressant-like activity well beyond the pharmacokinetic residence of the compound [4].

5-HT_{2A} mechanism confirmation in vivo: Volinanserin (0.125 mg/kg), a selective 5-HT_{2A} antagonist, completely blocked the FST immobility reduction produced by 2-Br-LSD in both sexes, without affecting locomotion [4]. This confirms that the antidepressant-like behavioral effects are 5-HT_{2A}-dependent.

6.4 Neuroplasticity

Dendritogenesis: In primary rat cortical neurons (DIV5-7), 2-Br-LSD at 1 to 10 micromolar produced dose-dependent increases in dendritic complexity measured by Sholl analysis and in total dendritic length [4]. The maximal effect at 10 micromolar was comparable to the positive control ketamine at 10 micromolar.

Spinogenesis: In mature primary rat cortical neurons (DIV18), 2-Br-LSD at 1 to 10 micromolar increased dendritic spine density at 24 hours post-treatment [4]. The effect at 10 micromolar was again comparable to ketamine.

Prefrontal cortex spine density in vivo: Single-dose 2-Br-LSD significantly increased dendritic spine density in the mouse prefrontal cortex compared to vehicle control (females: $t_{20} = 2.142$, $p = 0.045$; males: $t_{21} = 3.382$, $p = 0.003$) [4].

These neuroplasticity findings position 2-Br-LSD within the psychoplastogen class, a group of compounds (including psilocybin, LSD, MDMA, ketamine, and tabernanthalog) that promote structural synaptic remodeling as the basis for rapid

and sustained antidepressant effects.

6.5 Cardiovascular safety

The 5-HT_{2B} antagonism of 2-Br-LSD eliminates the cardiac valvulopathy risk associated with chronic 5-HT_{2B} agonism [4]. hERG channel inhibition, the principal in vitro proxy for QT prolongation risk, is weak for 2-Br-LSD (IC₅₀ 31.6 micromolar, approximately 77-fold above the IC₅₀ of astemizole at 0.41 micromolar) [4]. The compound demonstrates greater than 100-fold selectivity for serotonin and dopamine GPCRs over the hERG channel and other safety-relevant off-targets. The overall in vitro cardiovascular safety profile is favorable relative to both LSD and to ergoline derivatives with 5-HT_{2B} agonist activity.

7. Clinical Evidence Base

7.1 Cluster headache prophylaxis

The Karst, Halpern, Bernateck, and Passie (2010) open, non-randomized case series is the sole published clinical study of 2-Br-LSD [5]. Five male patients (ages 28 to 47; four chronic cluster headache, one episodic cluster headache) received three oral doses of BOL-148 at 30 micrograms per kilogram body weight (total doses approximately 2.0 to 3.1 mg) on days 1, 5, and 10.

Results by patient:

Patient S2 (episodic cluster headache): Cluster period terminated; sustained remission of six months and continuing at last follow-up [5].

Patient S3 (chronic): Pronounced reduction in attack frequency, including full remission for more than one month; at nine months post-treatment, ongoing remission of the cluster period [5].

Patient S5 (chronic): Pronounced reduction in attack frequency, including full remission for more than one month [5].

Patient S4 (chronic): Profound reduction in attack frequency without sustained full remission [5].

Patient S1 (chronic): Decrease in attack intensity of approximately 30 percent within the first four months, without major frequency reduction [5].

Adverse effects: Described as "very mild." Patients reported transient subjective effects ("flabby feeling," "light drunk," "funny" feeling) lasting 1 to 2 hours after each dose. No visual hallucinations, delusional thinking, or psychotic symptoms were observed. Vital signs (heart rate, blood pressure) remained unchanged throughout the treatment period [5].

The mechanism of cluster headache prophylaxis is not definitively established. The leading hypothesis invokes the 5-HT₁ pan-agonism (particularly 5-HT_{1B}/1D/1F activation) as the principal pharmacological basis, consistent with the broader observation that multiple serotonergic compounds with 5-HT₁ agonist activity (suma-

triptan, methysergide, LSD, psilocybin) modulate cluster headache pathophysiology [8]. The sustained duration of prophylactic effect (months beyond the pharmacokinetic residence of the compound) suggests a neuroplastic or neuromodulatory mechanism rather than simple receptor occupancy.

7.2 Historical human studies

Early Sandoz studies in the 1950s and 1960s administered BOL-148 to healthy volunteers and psychiatric patients in the context of LSD pharmacology research. These studies established that 2-Br-LSD lacks hallucinogenic activity at moderate to high doses and can partially block the psychedelic effects of subsequently administered LSD [6]. Formal clinical endpoints beyond subjective psychometric assessments were generally not measured. Some isolated reports documented hallucinogenic-like responses at very high doses, suggesting a dose threshold above which the partial agonist activity at 5-HT_{2A} may become sufficient for perceptual effects.

7.3 Ongoing development programs

No Phase 1 or later clinical trial results have been published for 2-Br-LSD as of the current monograph revision. BetterLife Pharma (BETR-001) received FDA pre-IND feedback in January 2022 and has been conducting IND-enabling studies [10]. Seaport Therapeutics (SPT-348) is conducting first-in-human-enabling studies for its prodrug formulation [11]. Clinical pharmacokinetic, safety, and efficacy data from these programs are anticipated but not yet available.

8. Sourcing and Quality Verification

Research-grade 2-Br-LSD is supplied by multiple chemical and pharmaceutical research suppliers. Cayman Chemical (catalog number 40633), MedChemExpress, Tocris, and other specialty suppliers provide the compound at greater than 95 percent purity by HPLC, typically in milligram quantities as the free base or as a salt form suitable for in vitro and in vivo research.

The compound is not a scheduled substance in the United States, Canada, Germany, or the European Union, and procurement for bona fide research purposes does not require a Drug Enforcement Administration Schedule I license (in contrast to LSD, which is Schedule I in the United States). This regulatory distinction substantially simplifies procurement, storage, and handling logistics for research laboratories.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 95 percent (greater than 98 percent preferred)
- Mass spectrometry confirmation of molecular weight and bromine isotope pattern (M and M+2 in approximately 1:1 ratio, diagnostic for mono-brominated compounds; expected [M+H]⁺ at 403.12)
- Nuclear magnetic resonance spectroscopy confirming the absence of the H-2 aromatic proton and the presence of characteristic indole ring proton shifts consistent with 2-substitution
- Chiral HPLC or optical rotation confirming the (6aR,9R) configuration and the absence of the inactive iso-lysergic acid epimer
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories (Janoshik Analytical and equivalent providers) offer independent verification of vendor certificates of analysis. Given the structural relationship to LSD, investigators should confirm that the material does not contain residual LSD, which would have regulatory and experimental implications.

Storage should be at -20 degrees Celsius, protected from light, under desiccation. The ergoline nucleus is photosensitive, and light exposure can produce degradation products that may confound pharmacological experiments.

9. Reconstitution and Handling

2-Bromo-LSD is supplied as a solid (crystalline or lyophilized powder) and is reconstituted for research use in appropriate solvents.

Stock solution preparation: The compound is soluble in dimethyl sulfoxide (DMSO) at concentrations of 10 to 50 mM for in vitro applications. For in vivo applications, dissolution in saline with a small percentage of DMSO (typically 5 to 10 percent v/v) or in acidified saline (0.1 percent tartaric acid in normal saline) is standard. The compound is also soluble in methanol and ethanol for analytical applications.

Working concentrations: In vitro neuroplasticity and receptor pharmacology assays typically employ concentrations of 0.1 nanomolar to 10 micromolar, with neuroplasticity effects observed at 1 to 10 micromolar and receptor binding and functional effects observed at sub-nanomolar to low-nanomolar concentrations [4]. In vivo behavioral studies in mice employ doses of 0.1 to 10 mg/kg administered intraperitoneally [4].

Storage of solutions: Aqueous and DMSO stock solutions should be stored at -20 degrees Celsius, protected from light, in amber glass vials or opaque containers. Aliquoting for single-use is recommended to minimize freeze-thaw cycles. The compound is expected to be stable through at least 5 freeze-thaw cycles in DMSO stock solution, though stability data specific to 2-Br-LSD have not been published; investigators should verify potency after extended storage by analytical methods.

Light protection: The ergoline chromophore is photosensitive. All handling, storage, and experimental work should employ amber glassware or aluminum foil wrapping, and exposure to direct sunlight or strong artificial light should be minimized. Degradation products from photolysis may include lysergic acid derivatives with altered receptor pharmacology.

Safety handling: Although 2-Br-LSD is non-hallucinogenic at moderate doses, it is a potent serotonin receptor ligand active at sub-nanomolar concentrations. Standard precautions for handling potent pharmacological compounds should be followed: gloves, safety glasses, fume hood use during weighing and dissolution, and avoidance of skin contact or inhalation of dry powder.

10. Stack Interactions and Combinations

2-Bromo-LSD interacts with multiple receptor systems and metabolic pathways. Investigators conducting research with the compound, particularly in combination pharmacology or in subjects receiving concurrent medications, should consider the following interactions:

Serotonergic agents: Concurrent use with serotonin reuptake inhibitors (SSRIs, SNRIs) may produce pharmacodynamic interactions at shared serotonin receptor targets. The 5-HT_{1A} agonism of 2-Br-LSD is additive with the indirect 5-HT_{1A} activation produced by SSRIs through elevated synaptic serotonin. Serotonin syndrome risk from 2-Br-LSD alone is low given its partial agonist and antagonist profile, but the combination with strong serotonergic agents warrants monitoring, particularly at higher doses.

Classical psychedelics and 5-HT_{2A} agonists: 2-Br-LSD acts as a functional antagonist at the 5-HT_{2A} receptor in the context of hallucinogenic responses, attenuating DOI-induced and presumably LSD-induced and psilocybin-induced HTR and psychedelic effects [4, 6]. Concurrent administration would be expected to produce pharmacological competition at the 5-HT_{2A} receptor, with the net effect depending on dose ratios and relative receptor kinetics.

Triptans and anti-migraine agents: The 5-HT_{1B/1D/1F} agonism of 2-Br-LSD overlaps mechanistically with sumatriptan, naratriptan, rizatriptan, and lasmiditan. Concurrent use may produce additive 5-HT₁-mediated vasoconstriction (for 5-HT_{1B}) or additive therapeutic effects at 5-HT_{1D} and 5-HT_{1F}. The interaction has not been formally characterized but is predictable from the shared receptor pharmacology.

CYP3A4 inhibitors and inducers: By analogy with LSD metabolism, 2-Br-LSD is expected to be a CYP3A4 substrate. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, grapefruit juice) may increase plasma concentrations; strong inducers (rifampin, carbamazepine, phenytoin) may reduce them. These interactions have not been formally characterized.

Dopamine receptor agents: The D2/D4 partial agonism of 2-Br-LSD may interact with antipsychotic medications (D2 antagonists), potentially reducing the receptor occupancy of the antipsychotic or, conversely, being blocked by the antipsychotic. Investigators studying 2-Br-LSD in patients receiving antipsychotic therapy should consider the impact of D2 receptor competition on both the efficacy of the antipsychotic and the pharmacological effects of 2-Br-LSD.

Ergot alkaloids: Concurrent use with other ergot derivatives (ergotamine, dihydroergotamine, methysergide, bromocriptine) may produce additive effects at shared serotonin and dopamine receptor targets and is generally avoided in clinical practice due to the risk of ergotism (peripheral vasoconstriction, digital ischemia) with combined ergoline dosing.

Beta-adrenergic blockers: The beta-1 and beta-2 adrenergic antagonism of 2-Br-LSD [4] may produce additive cardiovascular effects with concurrent beta-blocker therapy, including additive bradycardia and hypotension. This interaction is relevant because beta-blockers (propranolol, atenolol) are commonly used as prophylactic agents for cluster headache and migraine, the same indications under investigation for 2-Br-LSD.

11. Adverse Events and Safety Signal

11.1 Clinical adverse events

The adverse-event profile of 2-Br-LSD in humans is based on limited clinical exposure. In the Karst et al. (2010) case series (5 patients, 3 doses each), adverse effects were described as "very mild" and consisted of transient subjective sensations ("flabby feeling," "light drunk," "funny" feeling) lasting 1 to 2 hours after each oral dose [5]. No visual hallucinations, delusional thinking, psychotic symptoms, or clinically significant cardiovascular changes (heart rate, blood pressure) were observed. No serious adverse events were reported.

Historical studies from the 1950s and 1960s generally reported the absence of significant adverse effects at moderate doses, with isolated reports of hallucinogenic-like responses at very high doses.

11.2 Preclinical safety

Hallucinogenic liability: The absence of HTR across a 100-fold dose range and the inability of 5-HT1A or D2/D3 antagonism to unmask HTR provide strong preclinical evidence for the non-hallucinogenic profile [4]. However, the partial agonist activity at 5-HT2A (Emax approximately 60 percent) indicates that at sufficiently high doses or in pharmacologically sensitized individuals, some degree of perceptual alteration cannot be excluded.

Cardiac safety: The 5-HT2B antagonism eliminates valvulopathy risk [4]. Weak hERG inhibition (IC50 31.6 micromolar) indicates low QT prolongation risk [4]. No in vivo cardiovascular safety pharmacology data (telemetered ECG, blood pressure monitoring in conscious animals) have been published.

Cellular toxicity: No toxicity was detected in primary cortical neurons at concentrations producing maximal neuroplasticity effects (up to 10 micromolar) [4].

Tolerance and dependence: No tolerance was observed on seven-day repeated dosing [4]. Abuse potential and physical dependence have not been formally assessed in the standard FDA battery (self-administration, drug discrimination, phys-

ical dependence studies), though the absence of hallucinogenic and euphorogenic effects at therapeutic doses suggests low abuse potential.

11.3 Theoretical safety considerations

Serotonin syndrome: The multi-target serotonergic profile (5-HT1 agonism, 5-HT2A partial agonism, 5-HT6 agonism) creates a theoretical risk of serotonin syndrome in overdose or in combination with other serotonergic agents, particularly monoamine oxidase inhibitors. This risk has not been characterized preclinically or clinically.

Peripheral vasoconstriction: The 5-HT1B agonism shared with sumatriptan raises a theoretical concern for coronary and peripheral vasoconstriction in susceptible individuals (pre-existing coronary artery disease, Raynaud's phenomenon, peripheral vascular disease), a recognized safety consideration for the triptan class.

Reproductive safety: No reproductive or developmental toxicology data have been published for 2-Br-LSD. LSD has produced teratogenic effects in some animal studies at high doses; the applicability of these findings to 2-Br-LSD is unknown.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five serotonergic and lysergamide compounds against 2-Br-LSD, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to span the pharmacological space most relevant to the principal therapeutic applications of 2-Br-LSD (mood disorders, cluster headache, non-hallucinogenic psychoplastogenesis).

12.1 LSD (lysergic acid diethylamide)

Mechanism: Full or near-full agonist at 5-HT_{2A} (E_{max} approximately 92 percent), robust beta-arrestin recruitment, potent 5-HT_{2B} agonist, 5-HT₁ pan-agonist, D₁/D₂ agonist. Hallucinogenic.

Novelty: Low. LSD is the prototypical psychedelic compound and the parent molecule from which 2-Br-LSD is derived. Its pharmacology is extensively characterized across more than six decades of research.

Effect size: Large for acute psychedelic effects and for emerging clinical applications in mood disorders and cluster headache. Phase 2 trials of LSD for major depressive disorder and generalized anxiety disorder have demonstrated significant symptom reduction, though the effect is confounded by the psychedelic experience and associated expectancy effects [12].

Promising potential: Moderate to high. Multiple Phase 2 clinical programs are active for LSD in depression, anxiety, and headache disorders. However, the requirement for supervised psychedelic sessions, the hallucinogenic liability, and the Schedule I status in most jurisdictions impose substantial operational barriers to clinical adoption.

Side-effect profile: The principal liability is the hallucinogenic effect itself, which requires supervised clinical settings and carries risks of adverse psychological reactions (anxiety, panic, psychotic-like episodes) in vulnerable individuals.

Chronic 5-HT_{2B} agonism carries cardiac valvulopathy risk. hERG inhibition and QT prolongation risk are modest.

Overall validation: High. Extensive preclinical and emerging clinical evidence base. The hallucinogenic, regulatory, and cardiac safety liabilities are the principal limitations.

Comparison to 2-Br-LSD: 2-Br-LSD retains the 5-HT₁ pan-agonism and much of the receptor binding profile of LSD while eliminating the hallucinogenic activity (through reduced 5-HT_{2A} efficacy and beta-arrestin recruitment), the cardiac valvulopathy risk (through 5-HT_{2B} antagonism rather than agonism), and the regulatory scheduling. If the therapeutic effects of LSD in mood disorders and cluster headache can be dissociated from the psychedelic experience (a hypothesis supported by the cluster headache case series and the psychoplastogenesis data), 2-Br-LSD represents a more tractable therapeutic candidate.

12.2 Psilocybin

Mechanism: Prodrug of psilocin, a 5-HT_{2A/2C} agonist with moderate 5-HT_{1A} agonism. Hallucinogenic. Distinct chemical class (tryptamine vs. ergoline).

Novelty: Low. Psilocybin is the most extensively studied psychedelic in contemporary clinical trials.

Effect size: Large. Phase 2 and Phase 3 trials for treatment-resistant depression (COMPASS Pathways) and major depressive disorder (Usona Institute) have demonstrated substantial effect sizes (Cohen's $d > 1.0$ in some studies), though sustained effects require further characterization [13, 14].

Promising potential: High. FDA Breakthrough Therapy designation for treatment-resistant depression. Phase 3 trials underway. However, the requirement for supervised psychedelic sessions and therapist-assisted protocols limits scalability.

Side-effect profile: Acute psychedelic effects requiring clinical supervision. Transient cardiovascular changes (mild hypertension, tachycardia). No 5-HT_{2B} agonism (unlike LSD). Low cardiac safety risk. Psychological adverse events (anxiety, confusion, headache) reported in clinical trials.

Overall validation: High. The most advanced psychedelic in clinical development with extensive Phase 2/3 data.

Comparison to 2-Br-LSD: Psilocybin and 2-Br-LSD target overlapping but distinct receptor sets. Psilocybin (via psilocin) is a full 5-HT_{2A} agonist requiring supervised psychedelic sessions; 2-Br-LSD is a non-hallucinogenic partial agonist potentially suitable for unsupervised outpatient administration. The 5-HT₁ pan-agonism of 2-Br-LSD provides a pharmacological basis for cluster headache efficacy that psilocin lacks at comparable potency. The clinical evidence base for psilocybin is substantially larger, but 2-Br-LSD offers operational advantages (no psychedelic session, no scheduling barriers, potential for repeated dosing without tolerance).

12.3 Methysergide

Mechanism: Semi-synthetic ergoline; 5-HT_{2A/2B/2C} antagonist, 5-HT₁ partial agonist. Non-hallucinogenic. Historically used for migraine and cluster headache prophylaxis.

Novelty: Low. Methysergide was introduced in the 1960s and is a well-established (though now rarely used) migraine prophylactic.

Effect size: Moderate for migraine and cluster headache prophylaxis. Efficacy was established in multiple controlled trials in the 1960s and 1970s.

Promising potential: Low. The compound was withdrawn from most markets due to the risk of retroperitoneal, pleural, and cardiac valve fibrosis on chronic dosing, attributable to 5-HT_{2B} agonist metabolites (methylergonovine). It persists as a historical reference compound.

Side-effect profile: The fibrosis risk on chronic dosing (greater than 6 months) is the principal limitation and the reason for withdrawal. Acute side effects include nausea, dizziness, and leg cramps.

Overall validation: Moderate. Historically validated for headache prophylaxis but withdrawn for safety reasons.

Comparison to 2-Br-LSD: Both compounds are ergoline derivatives with 5-HT₁ agonist activity relevant to headache prophylaxis. 2-Br-LSD has the critical safety advantage of 5-HT_{2B} antagonism (rather than the agonism that produces fibrosis with methysergide metabolites). 2-Br-LSD additionally offers psychoplastogenic activity relevant to mood disorders, which methysergide lacks. The withdrawal of methysergide for fibrosis risk underscores the importance of the 5-HT_{2B} antagonist profile of 2-Br-LSD for any chronic or repeated dosing application.

12.4 Tabernanthalog (TBG)

Mechanism: Non-hallucinogenic ibogaine analogue; 5-HT_{2A} partial agonist, sigma-2 receptor ligand. Promotes psychoplastogenesis without hallucinogenic effects in mice (no HTR).

Novelty: High. TBG was designed de novo by the Bhatt and Bhatt laboratories (UC Davis, later Delix Therapeutics) as a non-hallucinogenic psychoplastogen, published in Nature (Olson, 2020) [15]. The ibogaine scaffold is structurally unrelated to the ergoline scaffold of 2-Br-LSD.

Effect size: Moderate in preclinical models. TBG promotes dendritogenesis in cortical neurons, produces antidepressant-like and anti-addictive behavioral effects in mice, and reduces ethanol self-administration in rodent models [15]. No clinical data are available.

Promising potential: Moderate. Delix Therapeutics is advancing TBG-derived compounds toward clinical development. The compound is earlier in development than 2-Br-LSD (no IND filing or pre-IND feedback as of the most recent monograph revision).

Side-effect profile: Favorable in preclinical studies. Non-hallucinogenic, non-cardiotoxic (no hERG liability at relevant concentrations). No clinical safety data.

Overall validation: Low to moderate. Strong preclinical data, no clinical data.

Comparison to 2-Br-LSD: Both compounds are non-hallucinogenic psychoplastogens that promote structural neuroplasticity through 5-HT_{2A}-dependent mechanisms. TBG is based on the ibogaine scaffold and was designed de novo for this purpose; 2-Br-LSD is a single-atom modification of an existing clinical compound (LSD) with a 70-year history of human exposure. 2-Br-LSD has the advantages of the 5-HT₁ pan-agonism (relevant to headache indications), the existing clinical case series data, the advanced regulatory status (pre-IND feedback), and the broader human safety record. TBG has the advantage of structural novelty and the absence of regulatory associations with controlled substances.

12.5 Lasmiditan

Mechanism: Selective 5-HT_{1F} agonist. Non-vasoconstrictor. FDA-approved for acute treatment of migraine (Reyvow, Eli Lilly).

Novelty: Moderate. Lasmiditan represents a novel mechanism in migraine (5-HT_{1F} selective agonism, the "ditan" class) distinct from the vasoconstrictor triptan mechanism (5-HT_{1B/1D}).

Effect size: Moderate for acute migraine treatment. Phase 3 trials demonstrated significant pain freedom and most-bothersome-symptom freedom at 2 hours compared to placebo.

Promising potential: Moderate. FDA-approved and commercially available but has not achieved widespread adoption due to CNS side effects (dizziness, sedation) and driving restrictions.

Side-effect profile: Dizziness (approximately 15 to 17 percent), somnolence, fatigue, paresthesia. No vasoconstrictor effects. Requires a driving restriction for 8 hours post-dose.

Overall validation: High. FDA-approved with extensive Phase 3 data.

Comparison to 2-Br-LSD: Lasmiditan is a selective 5-HT_{1F} agonist; 2-Br-LSD is a pan-5-HT₁ agonist with activity at 5-HT_{1A/1B/1D/1E/1F} plus 5-HT_{2A} partial agonism and additional receptor interactions. Lasmiditan is approved for acute migraine treatment; 2-Br-LSD is under investigation for cluster headache prophylaxis and mood disorders. The two compounds are not direct competitors but illustrate different pharmacological strategies within the 5-HT₁ target space. 2-Br-LSD offers broader receptor engagement and potential disease-modifying (neuroplastic) effects that lasmiditan does not; lasmiditan offers regulatory approval, 5-HT_{1F} selectivity, and a characterized human safety profile.

12.6 Comparator summary

The five comparators occupy distinct positions relative to 2-Br-LSD. **LSD** is the parent compound with extensive validation but carries hallucinogenic, cardiac, and regulatory liabilities that 2-Br-LSD eliminates. **Psilocybin** is the most clinically advanced psychedelic but requires supervised sessions and produces hallucinogenic effects. **Methysergide** is the historical precedent for ergoline headache prophylaxis but was withdrawn for fibrosis risk that 2-Br-LSD avoids through 5-HT_{2B} antagonism. **Tabernanthalog** is the closest mechanistic analogue as a non-hallucinogenic psychoplastogen but is earlier in development and lacks the 5-HT₁ headache-rele-

vant pharmacology. **Lasmiditan** validates the 5-HT_{1F} target for headache but is a selective acute treatment without disease-modifying or psychoplastogenic properties.

2-Br-LSD occupies a unique position in this landscape as the only compound that combines non-hallucinogenic psychoplastogenic activity (through biased 5-HT_{2A} partial agonism), elimination of cardiac valvulopathy risk (through 5-HT_{2B} antagonism), potent engagement of anti-migraine 5-HT₁ targets (through pan-5-HT₁ agonism), absence of tolerance on repeated dosing, unscheduled legal status, and a 70-year record of human exposure without serious adverse events. The principal limitation is the absence of Phase 1 or later clinical trial data from the contemporary development programs; the clinical evidence base rests entirely on the 2010 open-label case series of 5 cluster headache patients and on historical 1950s-1960s human exposure data. The compound's progression through IND-enabling studies by two independent pharmaceutical sponsors (BetterLife Pharma and Seaport Therapeutics) reflects the strength of the preclinical and mechanistic rationale and the breadth of the therapeutic opportunity across mood disorders, headache, and potentially additional neuropsychiatric indications.

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