

RESEARCH MONOGRAPH . COMPOUND PROFILE

Baclofen

A chlorophenyl-substituted gamma-aminobutyric acid analog developed at Ciba-Geigy as an antiepileptic candidate, repositioned as the prototypical GABA-B receptor agonist for the treatment of spasticity, and subsequently investigated for alcohol use disorder, gastroesophageal reflux, and neurodevelopmental conditions.

DOCUMENT	KDC-MN-1567
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Selective GABA-B receptor agonist with centrally and spinally mediated inhibitory activity

ABSTRACT

Baclofen (4-amino-3-(4-chlorophenyl)butanoic acid) is a lipophilic analog of gamma-aminobutyric acid (GABA) and the only clinically approved selective agonist of the GABA-B metabotropic receptor. Synthesized at Ciba-Geigy by Heinrich Keberle in 1962 as a candidate antiepileptic agent, the compound failed to demonstrate meaningful anticonvulsant activity in human trials but was found to reduce skeletal muscle spasticity through inhibition of monosynaptic and polysynaptic spinal reflexes. This observation led to regulatory approval in the United Kingdom in 1971 and by the United States Food and Drug Administration in 1977 for the treatment of spasticity of spinal origin, including that associated with multiple sclerosis and spinal cord injury. The introduction of intrathecal baclofen delivery by programmable pump in 1984, pioneered by Richard Penn and colleagues at Rush University, extended the therapeutic range to severe, refractory spasticity of both spinal and cerebral origin, including cerebral palsy and acquired brain injury; the intrathecal formulation received FDA approval in 1992.

The molecular pharmacology of baclofen is dominated by agonism at the GABA-B receptor, a heterodimeric G-protein-coupled receptor composed of GABA-B1 and GABA-B2 subunits that signals through Gi/Go proteins to activate inwardly rectifying potassium channels, inhibit voltage-gated calcium channels, and reduce adenylyl cyclase activity. These actions produce presynaptic inhibition of excitatory neurotransmitter release and postsynaptic hyperpolarization in the spinal cord, brainstem, and higher brain regions. Baclofen is marketed as a racemic mixture;

the (R)-enantiomer (arbaclofen) is approximately 100-fold more potent than the (S)-enantiomer at the GABA-B receptor and is responsible for essentially all pharmacological activity.

Pharmacokinetics after oral administration are characterized by rapid absorption (bioavailability 70 to 85 percent), peak plasma concentrations at 2 to 3 hours, minimal hepatic metabolism (approximately 15 percent, primarily by deamination), predominant renal excretion of unchanged drug (70 to 80 percent), and a short plasma elimination half-life of 2 to 4 hours that necessitates multiple daily dosing.

Beyond the registered spasticity indication, baclofen has been investigated extensively in alcohol use disorder, where GABA-B receptor agonism in the mesolimbic dopamine pathway reduces ethanol-seeking behavior and withdrawal severity. Sixteen randomized controlled trials have been conducted since the initial Addolorato et al. (2002) demonstration, with results that are encouraging but inconsistent across dose ranges and populations; France approved baclofen for alcohol dependence on a temporary basis in 2014. Additional research applications include gastroesophageal reflux disease (reduction of transient lower esophageal sphincter relaxations through GABA-B agonism on vagal afferents), trigeminal neuralgia, hiccups, and the R-enantiomer (arbaclofen) in autism spectrum disorder and fragile X syndrome. The compound has a well-characterized adverse-event profile dominated by sedation, drowsiness, and muscular weakness at therapeutic doses, with a clinically significant withdrawal syndrome (agitation, seizures, hyperthermia, rhabdomyolysis) on abrupt discontinuation and a toxicity profile in overdose that includes coma, respiratory depression, and paradoxical seizures. This monograph reviews the chemistry, synthesis, and stereochemistry of baclofen; the GABA-B receptor

pharmacology in molecular detail; the comprehensive human pharmacokinetic record; the clinical evidence base across spasticity, alcohol use disorder, gastroesophageal reflux, and investigational indications; the reconstitution, sourcing, and stack-interaction considerations for laboratory and clinical work; and a comparative assessment of five alternative antispasticity and GABA-B-active compounds against baclofen on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Baclofen.

Marketed names: Lioresal (Novartis, original brand; oral tablets and intrathecal injection), Gablofen (CNS Therapeutics/Saol Therapeutics; intrathecal solution), Kemstro (orally disintegrating tablet, discontinued), Lyflex (oral solution), Baclodol (generic markets), and numerous generic preparations worldwide.

Development codes: The compound was developed under the Ciba-Geigy internal program designation; no single canonical development code analogous to ICS 205-930 is used in the early literature. The compound is identified in the original Keberle patent and early pharmacology literature by its chemical name or by the trade name Lioresal [1].

Chemical Abstracts Service registry numbers: 1134-47-0 (racemic free acid), 69308-37-8 ((R)-enantiomer, arbaclofen), 63701-55-3 ((S)-enantiomer). The racemic form is the pharmaceutical and pharmacopoeial material.

International Union of Pure and Applied Chemistry name: 4-amino-3-(4-chlorophenyl)butanoic acid. The compound is a beta-(4-chlorophenyl)-substituted derivative of gamma-aminobutyric acid (GABA), in which the chlorophenyl group at the beta-carbon confers lipophilicity sufficient for blood-brain barrier penetration that the endogenous neurotransmitter GABA lacks.

1.2 Structural class and chemistry

Baclofen is a GABA analog belonging to the structural class of aryl-substituted gamma-amino acids. The chlorophenyl substituent at the 3-position (beta-carbon) of the butanoic acid chain distinguishes it from GABA itself and from other GABA analogs such as gabapentin (1-(aminomethyl)cyclohexaneacetic acid) and pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid), which act at the alpha-2-delta subunit of voltage-gated calcium channels rather than at the GABA-B receptor [2].

Molecular formula: C₁₀H₁₂ClNO₂.

Exact mass: 213.0557 g/mol (monoisotopic).

Molecular weight: 213.66 g/mol.

Physical properties: White to off-white crystalline powder. Slightly soluble in water (approximately 4.7 mg/mL at 25 degrees Celsius), freely soluble in dilute acid and dilute alkali, sparingly soluble in methanol and ethanol, practically insoluble in chloroform and diethyl ether. Melting point is approximately 206 to 211 degrees Celsius with decomposition. The compound is zwitterionic at physiological pH, with a pKa of approximately 3.9 (carboxylic acid) and approximately 9.6 (amino group).

Stereochemistry: Baclofen contains one stereocenter at the 3-position (beta-carbon) and is supplied pharmaceutically as the racemic mixture of (R)- and (S)-enantiomers. The (R)-(-)-enantiomer is the pharmacologically active form at the GABA-B receptor, with approximately 100-fold greater binding affinity than the (S)-(+)-enantiomer (IC₅₀ of 0.015 micromolar versus 1.77 micromolar for displacement of [3H]-baclofen from cerebellar GABA-B sites) [3]. The (R)-enantiomer has been developed independently as arbaclofen (STX209) for investigational use in autism spectrum disorder and fragile X syndrome. Investigators acquiring research-grade baclofen should note that the pharmaceutical material is racemic; enantiopure (R)-baclofen is available from specialized suppliers and should be confirmed by chiral chromatography if stereochemical specificity is required.

1.3 Synthesis

The original synthesis of baclofen proceeds through condensation of 4-chlorobenzaldehyde with two equivalents of ethyl acetoacetate, followed by alkaline hydrolysis and decarboxylation to yield the beta-(4-chlorophenyl)glutaric acid intermediate [1]. Subsequent dehydration, treatment with ammonia, and Hofmann rearrangement with alkaline hypobromite yields the racemic gamma-amino acid. Alternative published syntheses include: Michael addition of diethyl malonate to 4-chloro-beta-nitrostyrene followed by reduction and hydrolysis; Arndt-Eistert homologation of 4-chlorophenylglycine; and asymmetric catalytic routes to enantiopure (R)-baclofen using chiral rhodium or copper catalysts with prochiral substrates [4]. Industrial manufacture produces the racemic material by optimized variants of the Knoevenagel-decarboxylation or Michael addition routes, with the product purified by recrystallization from aqueous ethanol. Typical pharmaceutical-grade purity is greater than 99 percent by HPLC. The intrathecal formulation (Lioresal

Intrathecal, Gablofen) is a sterile, pyrogen-free, isotonic solution of baclofen in sodium chloride for injection, supplied in sealed glass ampoules or prefilled syringes at concentrations of 0.05 mg/mL (screening dose), 0.5 mg/mL, and 2 mg/mL.

2. Abstract

Baclofen is a selective agonist of the GABA-B metabotropic receptor, the only compound of this pharmacological class approved for clinical use, and the prototypical agent for the study of GABA-B receptor function in the central and peripheral nervous systems [5]. The compound was synthesized in 1962 by Heinrich Keberle at Ciba-Geigy as a lipophilic GABA analog intended to cross the blood-brain barrier and produce centrally mediated anticonvulsant effects. The antiepileptic hypothesis was not confirmed in clinical trials, but the observation that baclofen reduced spasticity in patients with neurological conditions led to regulatory approval for the treatment of spasticity of spinal origin, first in the United Kingdom (1971), then in multiple European jurisdictions, and subsequently by the United States Food and Drug Administration (1977).

The registered spasticity indication encompasses multiple sclerosis, spinal cord injury, and other spinal disorders characterized by increased muscle tone, painful flexor and extensor spasms, and clonus. Oral baclofen at doses of 15 to 80 mg daily (divided into three doses) reduces Ashworth scale spasticity scores and spasm frequency in 70 to 87 percent of patients with spinal spasticity in published open-label and placebo-controlled trials [6, 7]. The introduction of intrathecal baclofen delivery by programmable pump (Penn and Kroin, 1984) extended the therapeutic range to severe, refractory spasticity of both spinal and cerebral origin at intrathecal doses 100- to 1000-fold lower than oral doses (typical maintenance 100 to 900 micrograms per day), with FDA approval of the intrathecal formulation in 1992 [8].

Beyond spasticity, baclofen has been investigated in alcohol use disorder, where GABA-B receptor agonism in the ventral tegmental area and nucleus accumbens reduces mesolimbic dopamine release and attenuates ethanol reinforcement. The Addolorato et al. (2002) randomized controlled trial in 39 alcohol-dependent patients demonstrated significantly higher abstinence rates with baclofen 30 mg/day compared to placebo [9]. Subsequent trials have produced inconsistent results, with meta-analyses suggesting modest efficacy that may be dose-dependent, with higher doses (90 mg/day or above) appearing more effective than the initial 30 mg/day [10, 11]. France approved baclofen for alcohol dependence on a temporary authorization in 2014, and a full marketing authorization was granted in 2020 at doses up to 80 mg/day. Additional investigational applications include gastroesophageal reflux

disease (reduction of transient lower esophageal sphincter relaxations), trigeminal neuralgia, intractable hiccups, opioid withdrawal, and the (R)-enantiomer arbaclofen for autism spectrum disorder and fragile X syndrome.

The compound is well tolerated at therapeutic doses but has clinically significant safety considerations. Common adverse events include drowsiness (10 to 25 percent), dizziness (5 to 15 percent), weakness (5 to 15 percent), nausea, and fatigue. Abrupt discontinuation produces a withdrawal syndrome characterized by agitation, tachycardia, seizures, hyperthermia, and (in severe cases) rhabdomyolysis, multi-organ failure, and death; the syndrome is particularly dangerous with abrupt cessation of intrathecal delivery. Overdose produces coma, respiratory depression, hypothermia, bradycardia, and paradoxical seizures, with a reported lethal threshold in healthy adults at approximately 200 mg or greater of acute ingestion [12].

3. Discovery and Development History

3.1 Origin

Baclofen was synthesized by Heinrich Keberle at the Ciba-Geigy research laboratories in Basel, Switzerland, in 1962. The synthetic program was motivated by a lecture that Keberle attended at a Royal Society conference organized by Wilhelm Feldberg in London, where the role of gamma-aminobutyric acid as an inhibitory neurotransmitter in the central nervous system was discussed [1]. Keberle conceived a series of beta-aryl-halogenated GABA derivatives designed to cross the blood-brain barrier (which GABA itself cannot do owing to its high polarity and the absence of a lipophilic substituent) and to exert centrally mediated inhibitory effects. Baclofen (the 4-chlorophenyl derivative) was selected from this series on the basis of its favorable pharmacological profile in early animal testing.

3.2 Antiepileptic investigation and repositioning

The original development rationale was anticonvulsant therapy. Keberle and colleagues tested baclofen in animal seizure models and advanced the compound to early clinical investigation for epilepsy. The antiepileptic hypothesis was not supported by clinical results: the compound did not produce reproducible anticonvulsant effects in human trials. However, clinical investigators observed that patients receiving baclofen experienced reduced muscle tone and fewer involuntary spasms, particularly patients with concurrent spasticity from neurological conditions [1, 5]. This serendipitous observation redirected the development program toward spasticity.

3.3 Spasticity registration

Ciba-Geigy advanced baclofen through clinical development for spasticity in the late 1960s. The compound was patented in 1968 and received its first regulatory approval in the United Kingdom in 1971 for the treatment of spasticity of spinal origin. The United States Food and Drug Administration approved oral baclofen (marketed as Lioresal) in 1977. The approved indications included spasticity resulting from multiple sclerosis, spinal cord injury, spinal cord diseases, and other spinal

cord pathology. The compound rapidly became the first-line oral pharmacotherapy for spasticity in these conditions and has retained that position for more than five decades [6].

3.4 Intrathecal baclofen

The major therapeutic advance in baclofen development was the introduction of intrathecal delivery. Richard Penn and Jay Kroin at Rush University Medical Center in Chicago reported in 1984 and 1985 that intrathecal injection of baclofen produced profound and sustained spasticity reduction at doses 100- to 1000-fold lower than the effective oral dose, with substantially reduced systemic adverse events [8]. The approach exploited the limited blood-brain barrier penetration of oral baclofen (which, despite the chlorophenyl substituent, remains hydrophilic enough that only a fraction of oral dose reaches the central nervous system at effective concentrations) by delivering the drug directly into the cerebrospinal fluid. Programmable implantable pumps (Medtronic SynchroMed) enabled chronic intrathecal delivery with adjustable infusion rates. The FDA approved intrathecal baclofen (Lioresal Intrathecal) in 1992 for the treatment of severe spasticity of spinal origin and subsequently for spasticity of cerebral origin, including cerebral palsy [13]. The intrathecal formulation is now the standard of care for severe, refractory spasticity that is inadequately controlled by oral antispasticity agents.

3.5 Expansion to alcohol use disorder

The investigation of baclofen in alcohol use disorder originated with the hypothesis that GABA-B receptor agonism could reduce ethanol reinforcement by suppressing mesolimbic dopamine release. Preclinical work by Colombo et al. (2000) demonstrated that baclofen reduced alcohol self-administration in Sardinian alcohol-preferring rats [14]. The first randomized controlled trial was conducted by Addolorato et al. (2002) at the Catholic University of Rome, demonstrating significantly higher rates of complete abstinence (70 percent versus 21 percent) over 4 weeks in 39 alcohol-dependent patients receiving baclofen 30 mg/day versus placebo [9]. The personal narrative of French cardiologist Olivier Ameisen, who self-treated his alcohol dependence with high-dose baclofen and published his experience in 2005 and in a widely read 2008 book, catalyzed public interest and off-label prescribing, particularly in France [15]. Sixteen randomized controlled trials have since been com-

pleted, with heterogeneous results across doses and populations; the French regulatory authority ANSM granted a temporary recommendation for use (RTU) in 2014 and a full marketing authorization in 2020 [10, 11].

3.6 Arbaclofen development

The (R)-enantiomer of baclofen (arbaclofen, STX209) was developed by Seaside Therapeutics as a more pharmacologically refined version of baclofen for investigational use in fragile X syndrome and autism spectrum disorder. Phase 2 trials in fragile X syndrome demonstrated improvement in social avoidance and irritability measures, but the Phase 3 program did not meet its primary endpoint and Seaside Therapeutics ceased operations in 2013 [16]. Subsequent academic investigators have continued preclinical work with arbaclofen in 16p11.2 deletion syndrome and other neurodevelopmental conditions.

4. Mechanism of Action

Baclofen is a selective agonist of the GABA-B receptor, the metabotropic receptor for gamma-aminobutyric acid. The GABA-B receptor is a class C G-protein-coupled receptor that functions as an obligate heterodimer of GABA-B1 and GABA-B2 subunits [17].

4.1 GABA-B receptor structure and signaling

The GABA-B receptor heterodimer comprises the GABA-B1 subunit, which contains the orthosteric (GABA/baclofen) binding site in its extracellular Venus flytrap domain, and the GABA-B2 subunit, which couples to intracellular G proteins (Gi and Go classes). Neither subunit signals effectively alone; heterodimerization is required for surface expression, ligand binding, and G-protein activation [17, 18]. Two principal GABA-B1 splice variants exist: GABA-B1a (predominantly presynaptic, containing a pair of N-terminal sushi domains that mediate axonal targeting) and GABA-B1b (predominantly postsynaptic and dendritic). This differential localization underlies the dual presynaptic and postsynaptic actions of baclofen.

Activation of the GABA-B receptor by baclofen produces three principal intracellular signaling events through Gi/Go protein coupling: (a) activation of G-protein-coupled inwardly rectifying potassium (GIRK) channels, producing postsynaptic hyperpolarization and reduced neuronal excitability; (b) inhibition of voltage-gated calcium channels (principally N-type, P/Q-type, and R-type), reducing presynaptic calcium influx and consequently reducing neurotransmitter vesicle release; and (c) inhibition of adenylyl cyclase, reducing cyclic AMP production and modulating downstream protein kinase A activity [17, 18].

4.2 Spinal mechanisms

At the spinal cord level, baclofen produces its antispasticity effect through both presynaptic and postsynaptic inhibition. Presynaptic GABA-B receptors (GABA-B1a/B2 heterodimers) on the terminals of group Ia and group II muscle spindle afferents and on descending corticospinal and reticulospinal fibers reduce glutamate and substance P release onto alpha motor neurons and interneurons. Postsynaptic

GABA-B receptors (GABA-B1b/B2 heterodimers) on interneurons and motor neurons produce direct hyperpolarization through GIRK channel activation. The net effect is inhibition of both monosynaptic (stretch reflex) and polysynaptic (flexor withdrawal and crossed extensor) spinal reflexes, reducing the exaggerated reflex activity that constitutes clinical spasticity [5, 19].

4.3 Supraspinal mechanisms

In the brainstem and higher brain regions, GABA-B receptors are expressed at high density in the thalamus, hippocampus, cerebellum, cerebral cortex, and in nuclei of the mesolimbic dopamine pathway (ventral tegmental area, nucleus accumbens). Baclofen activation of GABA-B receptors in the ventral tegmental area inhibits dopaminergic neuron firing and reduces dopamine release in the nucleus accumbens, the mechanistic basis for the observed reduction in ethanol, cocaine, and nicotine reinforcement in preclinical models [14, 20]. In the dorsal motor nucleus of the vagus and in the nucleus tractus solitarius, GABA-B receptor activation reduces vagal efferent activity to the lower esophageal sphincter, reducing the rate of transient lower esophageal sphincter relaxations (the principal mechanism of gastroesophageal reflux) [21].

4.4 Stereoselectivity

The pharmacological activity of racemic baclofen resides almost entirely in the (R)-enantiomer. (R)-baclofen binds the orthosteric site of the GABA-B1 subunit with an IC₅₀ of approximately 0.015 micromolar for displacement of [3H]-baclofen from rat cerebellar membranes, while (S)-baclofen binds with an IC₅₀ of approximately 1.77 micromolar, a difference of approximately 100-fold [3]. In functional assays (GIRK channel activation, inhibition of electrically evoked neurotransmitter release), (R)-baclofen is similarly 50- to 100-fold more potent. The (S)-enantiomer is pharmacologically inert at clinically relevant concentrations of the racemate. The pharmaceutical racemate therefore delivers an effective (R)-baclofen dose of approximately half the total dose.

4.5 Peripheral GABA-B mechanisms

GABA-B receptors are also expressed on peripheral sensory neurons (dorsal root ganglion cells), on autonomic nerve terminals, and on smooth muscle of the gastrointestinal tract and lower esophageal sphincter. Activation of peripheral GABA-B

receptors on sensory neurons produces antinociception through activation of TEA-sensitive potassium channels [22]. Activation of GABA-B receptors on vagal afferents and on the lower esophageal sphincter reduces transient lower esophageal sphincter relaxation frequency, the mechanism underlying the clinical effect in gastroesophageal reflux disease [21].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Baclofen is absorbed from the gastrointestinal tract after oral administration, primarily from the small intestine via a saturable large neutral amino acid transport system. Bioavailability is approximately 70 to 85 percent at therapeutic doses (10 to 30 mg), though absorption becomes proportionally reduced at higher doses owing to the saturation of carrier-mediated transport [23, 24]. Time to peak plasma concentration (T_{max}) after oral administration is 2 to 3 hours. Peak plasma concentration (C_{max}) after a single 10 mg oral dose is approximately 180 to 400 ng/mL. Food does not meaningfully alter the extent of absorption but may delay T_{max}.

5.2 Distribution

Volume of distribution is approximately 0.7 to 1.0 L/kg, indicating predominantly extracellular distribution with moderate tissue partitioning. Plasma protein binding is low, approximately 30 percent [23, 24]. The compound crosses the blood-brain barrier, but central nervous system penetration after oral dosing is limited relative to plasma concentrations owing to the compound's hydrophilic character at physiological pH (the zwitterionic form predominates). Cerebrospinal fluid concentrations after oral dosing are approximately 10 to 20 percent of plasma concentrations at steady state. This limited CNS penetration is the pharmacokinetic rationale for intrathecal delivery in severe spasticity, where direct CSF administration achieves effective local concentrations at total daily doses of 100 to 900 micrograms (compared to oral doses of 30 to 80 mg) [8].

5.3 Metabolism

Hepatic metabolism of baclofen is minimal. Approximately 15 percent of an administered dose undergoes hepatic biotransformation, principally by oxidative deamination to the corresponding beta-(4-chlorophenyl)-4-hydroxybutyric acid metabo-

lite, which is pharmacologically inactive [23]. The cytochrome P450 system plays a negligible role in baclofen metabolism; consequently, the compound has minimal potential for CYP-mediated drug-drug interactions.

5.4 Elimination

Renal excretion is the predominant elimination pathway. Approximately 70 to 80 percent of an oral dose is excreted unchanged in urine; the remainder is excreted as the deaminated metabolite in urine and in feces [23, 24]. The plasma elimination half-life is 2 to 4 hours in adults with normal renal function, though some pharmacokinetic studies using combined serum and urine sampling have reported values up to 6 to 7 hours [24]. The short half-life necessitates three-times-daily dosing for oral administration to maintain therapeutic plasma concentrations.

Renal impairment substantially prolongs baclofen elimination. In patients with end-stage renal disease, the half-life extends to 12 to 16 hours or longer, and dose reduction or avoidance is recommended in severe renal insufficiency (creatinine clearance below 30 mL/min) [25]. Baclofen is removed by hemodialysis, which is relevant in the management of baclofen toxicity in renal failure patients.

5.5 Routes of administration

Oral: The standard route for mild to moderate spasticity and for investigational applications (alcohol use disorder, GERD). Tablets are available in 5 mg, 10 mg, 20 mg, and 25 mg strengths. Typical initial dose is 5 mg three times daily, titrated upward in increments of 5 mg per dose every 3 to 7 days to a maximum of 80 mg daily in divided doses (some clinicians use higher doses off-label, particularly for alcohol use disorder, where doses up to 300 mg/day have been studied) [10, 15].

Intrathecal: The standard route for severe, refractory spasticity. Administered via a surgically implanted programmable pump (Medtronic SynchroMed or equivalent) connected to a spinal catheter, typically with the catheter tip at the T10 to L1 level for lower extremity spasticity or at the C5 to T2 level for upper extremity and generalized spasticity. Screening is performed by bolus intrathecal injection (50 to 100 micrograms); responders proceed to pump implantation. Maintenance doses range from 100 to 900 micrograms per day, with some patients requiring up to 2000 micrograms per day [8, 13].

5.6 Special populations

Pediatric: Oral baclofen is used in children with spasticity from cerebral palsy and other neurological conditions at weight-based doses (typically starting at 2.5 mg three times daily, titrated to a maximum of 40 to 60 mg daily). Intrathecal baclofen is approved for children aged 4 years and older with severe spasticity of spinal or cerebral origin [13]. **Geriatric:** Elderly patients are more susceptible to sedation and confusion; lower starting doses and slower titration are recommended. **Renal impairment:** Dose reduction is required in moderate to severe renal insufficiency owing to the predominant renal excretion of unchanged drug [25]. **Hepatic impairment:** No dose adjustment is required, as hepatic metabolism is minimal. **Pregnancy:** Limited human data. Animal studies have shown skeletal abnormalities at high doses; the compound is rated FDA pregnancy category C. Use in pregnancy should be considered only when benefit outweighs risk.

6. Preclinical Pharmacology

6.1 Spinal spasticity models

Baclofen reduces spasticity in multiple preclinical models. In the decerebrate cat preparation, intrathecal baclofen produces dose-dependent suppression of monosynaptic and polysynaptic reflexes, with ED50 values in the range of 0.1 to 1 microgram for intrathecal administration [19]. In the rat spinal cord transection model, oral baclofen reduces spasm frequency and Ashworth-equivalent scores at doses corresponding to the human therapeutic range. The effect is stereoselective: (R)-baclofen produces the full antispasticity effect, while (S)-baclofen is inactive at equivalent doses [3].

6.2 Alcohol self-administration models

Baclofen reduces ethanol self-administration in multiple preclinical models. Colombo et al. (2000) demonstrated that baclofen (1 to 3 mg/kg intraperitoneal) dose-dependently reduced ethanol intake in Sardinian alcohol-preferring (sP) rats without affecting water or food intake [14]. Subsequent studies confirmed reductions in ethanol self-administration, relapse-like drinking, and binge-like drinking in both rat and primate models. The mechanism is attributed to GABA-B receptor activation in the ventral tegmental area, reducing dopaminergic neuron firing and dopamine release in the nucleus accumbens [20].

6.3 Gastroesophageal reflux models

In the dog and ferret models of gastroesophageal reflux, baclofen reduces the rate of transient lower esophageal sphincter relaxations by 40 to 60 percent at doses that do not produce central sedation when administered peripherally [21]. The mechanism is mediated by GABA-B receptors on vagal afferent fibers and on neurons of the nucleus tractus solitarius.

6.4 Neurodevelopmental models

(R)-baclofen (arbaclofen) has been studied in mouse models of fragile X syndrome (Fmr1 knockout mice) and 16p11.2 deletion syndrome. In Fmr1 knockout mice, arbaclofen corrected elevated protein synthesis, reduced audiogenic seizure susceptibility, and normalized social behavior and marble-burying stereotypy [16]. In the 16p11.2 deletion mouse model, arbaclofen reduced hyperactivity and improved nest-building and social behavior [26].

7. Clinical Evidence Base

7.1 Spasticity of spinal origin

The registered and most extensively validated indication for oral baclofen is spasticity of spinal origin, including that resulting from multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, and other spinal cord diseases.

In multiple sclerosis, the double-blind crossover trial by Sachais et al. (1977) and the three-year follow-up study by Feldman et al. (1978) demonstrated significant reductions in spasticity (Ashworth scale), spasm frequency, and associated pain compared to placebo, with effects maintained over long-term use [6, 7]. Open-label studies have reported improvement in 70 to 87 percent of patients with spinal spasticity. Comparative trials with diazepam have demonstrated similar antispasticity efficacy but fewer sedative adverse effects with baclofen [27].

In spinal cord injury, placebo-controlled trials have demonstrated statistically significant improvements in Ashworth spasticity scores and spasm frequency. The benefit extends to functional outcomes: patients report improved activities of daily living, reduced pain, and improved sleep [28].

7.2 Intrathecal baclofen for severe spasticity

Penn and Kroin (1985) reported the first clinical series of intrathecal baclofen for severe spasticity refractory to oral medication [8]. Subsequent randomized, placebo-controlled trials in patients with spinal cord injury and multiple sclerosis demonstrated superiority of intrathecal baclofen over intrathecal placebo on both the Ashworth scale and spasm frequency score [29]. The Ontario Health Technology Assessment Series (2005) conducted a meta-analysis of the intrathecal baclofen evidence base and concluded that the evidence supported efficacy for severe spasticity of spinal and cerebral origin, with meaningful improvements in quality of life and functional capacity [13].

Intrathecal baclofen has also been validated for spasticity of cerebral origin, including cerebral palsy, acquired brain injury, and stroke. In children with cerebral palsy, a systematic review and meta-analysis (2015) confirmed statistically signifi-

cant reductions in spasticity and small but significant improvements in motor function [30]. Long-term follow-up studies extending to 10 and 15 years have demonstrated sustained efficacy, though catheter-related complications (kinking, migration, breakage), pump malfunction, and infection occur in 10 to 40 percent of patients over the lifetime of the system [31].

7.3 Alcohol use disorder

The clinical evidence for baclofen in alcohol use disorder has accumulated through 16 randomized controlled trials since the initial Addolorato et al. (2002) demonstration [9]. Key trials include:

Addolorato et al. (2007) replicated the initial findings in 84 alcohol-dependent patients with comorbid liver cirrhosis, demonstrating significantly higher abstinence rates (71 percent versus 29 percent) with baclofen 30 mg/day compared to placebo over 12 weeks, with the added demonstration of safety in patients with decompensated liver disease [32].

Muller et al. (2015, BACLAD study) randomized 56 alcohol-dependent patients to baclofen 30 mg/day, 90 mg/day, or placebo for 12 weeks and reported that the 90 mg/day dose produced significantly higher abstinence rates than placebo, while 30 mg/day did not [33].

Reynaud et al. (2017, ALPADIR study) randomized 320 alcohol-dependent patients in France to baclofen (target dose 180 mg/day, maximum 300 mg/day) or placebo for 24 weeks and found no significant difference in the primary endpoint of complete abstinence, though secondary endpoints favored baclofen [34].

Leggio et al. (2021) conducted a dose-response trial in 120 U.S. patients randomized to placebo, 30 mg/day, or 90 mg/day for 12 weeks and found a significant main effect of baclofen driven by the 90 mg/day dose on percent heavy drinking days [10].

The aggregate evidence from meta-analyses suggests modest efficacy of baclofen in reducing alcohol consumption and promoting abstinence, with effect sizes that are dose-dependent and more consistently positive at doses of 60 mg/day or higher [11]. The inconsistency across trials has been attributed to dose heterogeneity, differences in outcome definitions, population heterogeneity (severity of alcohol de-

pendence, comorbid liver disease), and the limited blood-brain barrier penetration of oral baclofen at standard doses. France remains the only jurisdiction with a specific regulatory authorization for baclofen in alcohol dependence.

7.4 Gastroesophageal reflux disease

Baclofen reduces the rate of transient lower esophageal sphincter relaxations (TLESRs), the principal mechanism of gastroesophageal reflux, by 40 to 60 percent. A meta-analysis of randomized controlled trials (Bortoli et al. 2014) confirmed that baclofen significantly reduced TLESR frequency, acid reflux episodes, and reflux symptoms compared to placebo [21, 35]. Doses of 10 to 20 mg three times daily have been used. The clinical utility is limited by the short half-life (requiring frequent dosing), by sedation at effective doses, and by the availability of proton pump inhibitors as first-line therapy. The GABA-B agonist lesogaberan (AZD3355), developed by AstraZeneca as a peripherally restricted GABA-B agonist for GERD, reached Phase 2b trials but failed to demonstrate clinically meaningful symptom improvement despite significant TLESR reduction and was discontinued [36].

7.5 Trigeminal neuralgia

Baclofen has been used as second-line or adjunctive therapy for trigeminal neuralgia, typically at doses of 30 to 60 mg daily. The evidence base consists of small controlled trials and case series. A double-blind crossover trial by Fromm et al. (1984) in 10 patients with trigeminal neuralgia demonstrated significant pain reduction with baclofen versus placebo [37]. The mechanism is attributed to GABA-B receptor activation in the trigeminal nucleus caudalis, reducing excitatory transmission in the nociceptive pathway.

7.6 Intractable hiccups

Baclofen at doses of 15 to 45 mg daily has been reported effective for intractable hiccups in case series and small controlled trials. The mechanism involves GABA-B receptor activation on the phrenic nerve reflex arc and on brainstem hiccup center neurons. A controlled trial by Zhang et al. (2014) demonstrated significant reduction in hiccup frequency and severity with baclofen versus placebo [38].

7.7 Fragile X syndrome and autism spectrum disorder

The (R)-enantiomer arbaclofen (STX209) was investigated by Seaside Therapeutics in Phase 2 and Phase 3 trials for fragile X syndrome and autism spectrum disorder. The Phase 2 trial in 63 fragile X syndrome subjects demonstrated improvement in social avoidance (the prespecified primary endpoint in the group with high baseline social avoidance) and in the clinician-rated Clinical Global Impression scale [16]. The subsequent Phase 3 trial in 125 subjects did not meet its primary endpoint (Aberrant Behavior Checklist-Social Avoidance subscale) and the program was discontinued. A separate Phase 2 trial of arbaclofen in autism spectrum disorder (without fragile X) was initiated but terminated prior to completion following the Seaside Therapeutics closure [39].

8. Sourcing and Quality Verification

Pharmaceutical-grade baclofen is widely available as oral tablets (5 mg, 10 mg, 20 mg, 25 mg), oral solution (5 mg/5 mL), and intrathecal injection (0.05, 0.5, and 2 mg/mL). The compound is manufactured by numerous generic pharmaceutical companies worldwide. Oral baclofen is inexpensive (typically less than \$0.20 per 10 mg tablet in the United States generic market).

Research-grade baclofen is supplied by major chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress, Abcam) as the racemic free acid at greater than 98 percent purity by HPLC. Enantiopure (R)-baclofen (arbaclofen) is available from specialized suppliers (Tocris, Sigma-Aldrich) at comparable purity. Pricing is moderate (approximately \$20 to \$80 per gram for racemic research-grade material).

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

- High-performance liquid chromatography area-percent purity (greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (214.06 for the protonated molecular ion $[M+H]^+$)
- Chiral HPLC or polarimetry if enantiomeric composition is relevant to the study
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis for common synthesis solvents

The pharmaceutical baclofen market is well established, generic competition is extensive, and counterfeit material is uncommon. Investigators using pharmaceutical-grade oral tablets for research can rely on the USP or European Pharmacopoeia monograph specifications without additional analytical confirmation, though on-receipt identity testing is reasonable practice for any investigation requiring dosing precision.

9. Reconstitution and Handling

Baclofen is supplied as a crystalline powder (research grade) or as finished pharmaceutical forms (oral tablets, oral solution, intrathecal injection). The compound is stable in the solid state at room temperature; storage at controlled room temperature (15 to 30 degrees Celsius) with protection from moisture is recommended. No special light protection is required.

For in vitro research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM, or in dilute hydrochloric acid (0.1 N HCl) or dilute sodium hydroxide (0.1 N NaOH) at lower concentrations. Aqueous solubility of the free acid is limited (approximately 4.7 mg/mL at 25 degrees Celsius, pH-dependent); solubility increases substantially in acidic or basic solution owing to the zwitterionic character. DMSO stock solutions are stable for at least 6 months at -20 degrees Celsius; aqueous solutions should be used within 7 days of preparation or aliquoted and frozen at -20 degrees Celsius.

The intrathecal formulation (Lioresal Intrathecal, Gablofen) is a sterile, isotonic solution in sodium chloride for injection. It must be handled aseptically and is intended exclusively for intrathecal administration via an implanted pump or for screening test doses via lumbar puncture. The solution is stable at controlled room temperature and should not be frozen. Once the pump reservoir is filled, the contents are stable at body temperature for the duration of the refill interval (typically 1 to 6 months depending on dose and concentration).

Oral tablets are stable through their labeled expiration date when stored at controlled room temperature. Crushed tablets suspended in water for administration via nasogastric or gastrostomy tube are commonly prepared in clinical practice; stability data for crushed tablet suspensions are limited, and use within 1 hour of preparation is recommended.

10. Stack Interactions and Combinations

Baclofen interacts with several drug classes through its GABAergic mechanism and through additive central nervous system depressant effects. Investigators conducting research with baclofen should consider:

Central nervous system depressants: Concurrent use with benzodiazepines, opioids, barbiturates, ethanol, sedating antihistamines, and general anesthetics produces additive sedation, respiratory depression, and hypotension. This interaction is the most clinically important and is the principal safety consideration in patients receiving oral baclofen for any indication. The combination of baclofen and opioids has been associated with increased risk of respiratory failure and death [40].

Other antispasticity agents: Concurrent use with tizanidine (alpha-2 adrenergic agonist), dantrolene (ryanodine receptor antagonist), or diazepam produces additive antispasticity effects but also additive sedation and weakness. Combination therapy is used clinically when monotherapy is inadequate, but requires careful dose titration and monitoring [27].

Antihypertensive agents: Baclofen can reduce blood pressure through central sympatholytic and GABA-B-mediated mechanisms. Concurrent use with antihypertensive medications may produce additive hypotension, particularly in elderly patients.

Tricyclic antidepressants: Concurrent use has been reported to potentiate the muscle-relaxant effect of baclofen and to increase the risk of muscular hypotonia. Dose reduction of one or both agents may be required.

Monoamine oxidase inhibitors: Theoretical concern for additive hypotensive effects; clinical data are limited.

Renal-clearance-dependent drugs: As baclofen is predominantly renally excreted, drugs that reduce renal function (nonsteroidal anti-inflammatory drugs, aminoglycosides, angiotensin-converting enzyme inhibitors) may increase baclofen exposure by reducing its clearance. This interaction is principally relevant in patients with pre-existing renal impairment [25].

Levodopa and dopaminergic agents: Concurrent use with levodopa/carbidopa in Parkinson's disease patients may produce additive confusion and hallucinations. Baclofen has also been reported to reduce the efficacy of levodopa in some patients.

Lithium: Case reports of exacerbated hyperkinetic symptoms with concurrent baclofen and lithium therapy.

GABA-B positive allosteric modulators: Concurrent administration with investigational GABA-B positive allosteric modulators (CGP7930, GS39783, ADX71441) produces synergistic GABA-B receptor activation in preclinical models. The combination may allow dose reduction of baclofen to reduce adverse events while maintaining efficacy, an approach under investigation for alcohol use disorder and spasticity [41].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at therapeutic oral doses (30 to 80 mg daily) are:

- Drowsiness and sedation (10 to 25 percent)
- Dizziness (5 to 15 percent)
- Weakness and fatigue (5 to 15 percent)
- Nausea (4 to 8 percent)
- Headache (4 to 8 percent)
- Constipation (2 to 6 percent)
- Insomnia or sleep disturbance (2 to 7 percent)
- Urinary frequency or retention (2 to 6 percent)
- Confusion and cognitive impairment (1 to 5 percent, higher in elderly)

These adverse events are dose-dependent and generally manageable with dose titration. Sedation and drowsiness are the most common reasons for dose limitation or discontinuation [6, 23].

11.2 Withdrawal syndrome

Abrupt discontinuation of baclofen, whether oral or intrathecal, produces a potentially life-threatening withdrawal syndrome. The syndrome typically manifests 24 to 48 hours after dose reduction or cessation and includes agitation, anxiety, confusion, hallucinations, seizures, tachycardia, hyperthermia, hypertension or hypotension, muscle rigidity (rebound spasticity), and (in severe cases) rhabdomyolysis, disseminated intravascular coagulation, multi-organ failure, and death [12, 42]. The withdrawal syndrome resembles serotonin syndrome and neuroleptic malignant syndrome in its presentation and requires distinction from these conditions.

Intrathecal baclofen withdrawal is particularly dangerous and can be precipitated by pump malfunction, catheter disconnection or obstruction, battery depletion, or human error in refilling. All patients with intrathecal baclofen pumps and

their caregivers should be educated about the signs of withdrawal, and emergency oral baclofen should be available. Management includes reinstitution of baclofen at therapeutic doses, benzodiazepines for seizures and agitation, dantrolene for hyperthermia and rigidity, and supportive intensive care [42].

11.3 Overdose and toxicity

Baclofen overdose produces central nervous system depression (coma, respiratory depression), hypothermia, bradycardia, hypotension, flaccidity, and mydriasis. Paradoxical seizures occur in approximately 36 percent of overdose cases, likely mediated by disinhibition of excitatory circuits through pre- and postsynaptic GABA-B mechanisms [12]. Toxicity has been reported with acute ingestions of 200 mg or greater in adults. Intrathecal overdose (typically from pump malfunction or programming error) produces the same syndrome at much lower absolute doses (1.5 mg or greater) owing to the direct cerebrospinal fluid exposure.

Treatment of overdose is supportive: airway management, mechanical ventilation for respiratory depression, atropine for symptomatic bradycardia, vasopressors for refractory hypotension, and benzodiazepines for seizures. There is no specific antidote. Hemodialysis removes baclofen and is recommended in severe toxicity with renal impairment [12].

11.4 Long-term safety

Long-term use of oral baclofen at therapeutic doses has been documented over decades in spasticity populations without evidence of cumulative organ toxicity. Hepatotoxicity is rare and idiosyncratic. Cognitive impairment and mood disturbance (depression, euphoria) are reported in long-term users, particularly at higher doses. Tolerance to the antispasticity effect may develop over months to years, though this is not consistently observed.

11.5 Pregnancy and lactation

Animal studies have demonstrated skeletal abnormalities (omphaloceles, incomplete sternebral ossification) at doses approximately 10 times the maximum recommended human dose. Human pregnancy data are limited to case reports and small series. The compound crosses the placenta. It is classified as FDA pregnancy cate-

gory C. Baclofen is excreted in breast milk at low concentrations; the American Academy of Pediatrics has classified it as compatible with breastfeeding, though caution is advised.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative anti-spasticity and GABA-B-active compounds against baclofen, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or in vitro), and overall validation. The five candidates were selected as the principal pharmacological alternatives to baclofen for the treatment of spasticity and as representative GABA-B active compounds with clinical or advanced preclinical data.

12.1 Tizanidine

Mechanism: Centrally acting alpha-2 adrenergic agonist. Reduces spasticity by increasing presynaptic inhibition of motor neurons at the spinal level through activation of alpha-2 adrenoceptors on spinal interneurons, reducing the release of excitatory amino acids. The mechanism is distinct from the GABA-B pathway of baclofen [43].

Development trajectory: Developed by Sandoz (now Novartis) and approved by the FDA in 1996 for the management of spasticity associated with multiple sclerosis and spinal cord injury. Marketed as Zanaflex. Available as 2 mg and 4 mg tablets and capsules.

Novelty: Low. Alpha-2 adrenergic agonism for spasticity is a well-established mechanism; tizanidine is the second generation after clonidine with improved tolerability.

Effect size: Comparable to baclofen on Ashworth scale spasticity scores in head-to-head trials. A meta-analysis by Groves et al. (1998) found no significant difference in antispasticity efficacy between tizanidine and baclofen across multiple controlled trials [44]. Tizanidine may preserve muscle strength to a greater degree than baclofen, which is clinically relevant for ambulatory patients.

Promising potential: Stable. The compound is established in clinical practice as a first-line alternative to baclofen. No new indications or substantial clinical development programs are in progress.

Side-effect profile: The principal adverse events are dry mouth (approximately 50 percent), drowsiness (approximately 48 percent), dizziness, and asthenia. Hepatotoxicity (elevated transaminases) occurs in approximately 5 percent of patients and is the principal serious adverse event; liver function monitoring is recommended during treatment. Tizanidine produces more dry mouth but less weakness than baclofen; the overall adverse event rates are similar [43, 44].

Overall validation: High. The compound has an extensive clinical evidence base, regulatory approval in major jurisdictions, and a well-characterized safety profile over decades of clinical use.

Comparison to baclofen: Tizanidine and baclofen have comparable antispasticity efficacy with different side-effect profiles. Tizanidine is preferred in ambulatory patients where preservation of muscle strength is important; baclofen is preferred when sedation tolerance exists, when GABA-B-mediated effects are desired (e.g., concurrent alcohol use disorder), or when intrathecal delivery is required (tizanidine has no intrathecal formulation).

12.2 Dantrolene

Mechanism: Direct-acting skeletal muscle relaxant. Dantrolene binds the ryanodine receptor (RyR1) on the sarcoplasmic reticulum, reducing calcium release and consequently reducing muscle contraction force. The mechanism is peripheral and does not involve central nervous system GABA or adrenergic pathways [45].

Development trajectory: Developed by Eaton Laboratories and approved by the FDA in 1974 for spasticity and in 1979 for malignant hyperthermia. Marketed as Dantrium (oral capsules and intravenous formulation).

Novelty: Low. The ryanodine receptor mechanism has been established for over 50 years.

Effect size: Evidence for antispasticity efficacy is of lower quality than for baclofen or tizanidine. Controlled trials have shown reductions in spasticity, but the evidence is rated as poor quality in systematic reviews [44]. The compound is more

clearly established for malignant hyperthermia, where it is the only specific pharmacological treatment.

Promising potential: Low for spasticity. Stable for malignant hyperthermia. No new development programs in progress for either indication.

Side-effect profile: Hepatotoxicity is the most significant concern, with symptomatic hepatitis reported in 0.35 to 1 percent of patients and fatal hepatic necrosis in rare cases (approximately 0.1 to 0.2 percent with prolonged use). Other adverse events include drowsiness, diarrhea (which can be dose-limiting), weakness, and fatigue. The hepatotoxicity risk is greater than that of baclofen or tizanidine and limits long-term use [45].

Overall validation: Moderate for spasticity (limited by evidence quality and hepatotoxicity). High for malignant hyperthermia.

Comparison to baclofen: Baclofen has stronger clinical evidence, a better safety profile, and greater versatility (multiple routes of administration, broader clinical applications) than dantrolene for spasticity. Dantrolene has the advantage of a purely peripheral mechanism that avoids CNS depression but carries meaningful hepatotoxicity risk. The two agents are sometimes combined at reduced doses to exploit complementary mechanisms.

12.3 Diazepam

Mechanism: Benzodiazepine acting at the GABA-A receptor. Diazepam enhances GABA-A receptor chloride channel conductance by binding the benzodiazepine allosteric site, producing increased inhibitory postsynaptic potentials at spinal interneurons. The antispasticity effect is mediated by increased presynaptic inhibition at the spinal cord level [46].

Development trajectory: Developed by Hoffmann-La Roche and introduced in 1963 for anxiety disorders. Antispasticity use is an established off-label and labeled application in some jurisdictions.

Novelty: Very low. Benzodiazepine pharmacology for spasticity is the oldest pharmacological approach and is well established.

Effect size: Comparable to baclofen and tizanidine on Ashworth scale measures in controlled trials [27]. Effective for reducing spasm frequency and nocturnal spasticity.

Promising potential: Low. No new development programs. The compound remains in clinical use as a second-line or adjunctive agent.

Side-effect profile: Sedation, cognitive impairment, dependence (tolerance and withdrawal), ataxia, and paradoxical disinhibition. The dependence liability and cognitive effects are substantially greater than those of baclofen and are the principal reasons that baclofen has displaced diazepam as first-line antispasticity therapy [27, 46].

Overall validation: High for antispasticity efficacy. Low for the side-effect profile relative to modern alternatives.

Comparison to baclofen: Baclofen is preferred over diazepam for most spasticity applications owing to the lower risk of dependence, less cognitive impairment, and the availability of intrathecal delivery. Diazepam is used adjunctively for nocturnal spasticity or when rapid-onset anxiolysis is concurrently desired.

12.4 Arbaclofen (STX209)

Mechanism: The (R)-enantiomer of baclofen, the pharmacologically active component at the GABA-B receptor. Arbaclofen has approximately 100-fold greater potency than (S)-baclofen and delivers GABA-B agonism without the pharmacologically inert (S)-enantiomer present in racemic baclofen [3].

Development trajectory: Developed by Seaside Therapeutics for fragile X syndrome and autism spectrum disorder. Phase 2 trials in fragile X demonstrated improvement in social avoidance; Phase 3 trial (125 subjects) failed to meet its primary endpoint. Seaside Therapeutics ceased operations in 2013. Academic investigation continues for 16p11.2 deletion syndrome and other neurodevelopmental conditions [16, 26, 39].

Novelty: Low to moderate. The enantiopure strategy is a refinement rather than a novel pharmacological concept. The application to neurodevelopmental disorders was novel at the time of development.

Effect size: Phase 2 signals in fragile X syndrome were modest (significant in the subgroup with high baseline social avoidance) but did not replicate at Phase 3 scale. No comparative antispasticity data exist, as arbaclofen was not developed for spasticity.

Promising potential: Low to moderate. Active development has ceased. Ongoing academic preclinical work maintains interest in neurodevelopmental applications. The enantiopure approach could in principle reduce the total drug burden by half for any baclofen indication, but this has not been clinically pursued for spasticity or alcohol use disorder.

Side-effect profile: Phase 2 data suggested a safety profile similar to racemic baclofen at equivalent (R)-baclofen exposures.

Overall validation: Low. Clinical development was terminated after Phase 3 failure. The compound serves primarily as a research tool.

Comparison to baclofen: Arbaclofen provides the pharmacologically active enantiomer of baclofen without the inactive ballast of the (S)-enantiomer. In principle this could reduce off-target effects or improve the therapeutic index, but this advantage has not been demonstrated in clinical practice. Racemic baclofen remains the established pharmaceutical product with decades of clinical validation; arbaclofen is a research compound with a failed Phase 3 program.

12.5 Lesogaberan (AZD3355)

Mechanism: Peripherally restricted GABA-B receptor agonist designed for gastroesophageal reflux disease. The compound was developed by AstraZeneca to exploit the TLESR-reducing effect of GABA-B agonism without the central nervous system sedation of baclofen [36].

Development trajectory: Advanced through Phase 1 and Phase 2a trials with demonstrations of TLESR reduction and reflux suppression. Phase 2b trials failed to show clinically meaningful improvement in GERD symptoms despite significant TLESR reduction, and the development program was discontinued [36].

Novelty: Moderate. The peripherally restricted GABA-B agonist concept was a pharmacologically rational innovation designed to address the principal limitation of baclofen (CNS sedation) for the GERD application.

Effect size: Significant reduction in TLESRs (approximately 30 to 40 percent) but insufficient symptomatic improvement in GERD patients compared to placebo in Phase 2b.

Promising potential: Very low. Development is terminated. The compound serves as a reference for the concept that peripheral GABA-B agonism alone is insufficient for symptomatic GERD management.

Side-effect profile: Well tolerated in Phase 1 and Phase 2 trials, with minimal CNS adverse events consistent with the peripherally restricted design.

Overall validation: Low. The compound demonstrated proof of mechanism (TLESR reduction) but failed proof of concept (symptom improvement).

Comparison to baclofen: Lesogaberan was designed specifically to overcome baclofen's CNS limitation for the GERD application. The failure at Phase 2b suggests that either the TLESR reduction was insufficient in magnitude, or that GERD symptom relief requires contributions from central GABA-B pathways (or from non-GABA-B mechanisms), or both. Baclofen remains the only GABA-B agonist with demonstrated clinical efficacy in GERD, though its use is limited by sedation and the need for frequent dosing.

12.6 Comparator summary

The five compounds occupy distinct positions relative to baclofen. **Tizanidine** is the principal alternative first-line oral antispasticity agent with comparable efficacy, a different side-effect profile (more dry mouth, less weakness), and the advantage of preserving muscle strength, but without intrathecal delivery or GABA-B-mediated effects on alcohol reinforcement or esophageal function. **Dantrolene** provides a purely peripheral mechanism (ryanodine receptor) that avoids CNS depression but carries hepatotoxicity risk and has weaker clinical evidence for spasticity. **Diazepam** is effective but limited by dependence liability and cognitive impairment, making it a second-line or adjunctive option. **Arbaclofen** is the pharmacologically refined enantiopure form of baclofen with a failed Phase 3 program in fragile X syndrome and no registration for any indication. **Lesogaberan** is the peripherally restricted GABA-B agonist concept for GERD that failed at Phase 2b despite achieving the intended mechanism.

Baclofen occupies a unique and enduring position in this landscape: it is the only approved GABA-B receptor agonist, the only antispasticity agent with both oral and intrathecal formulations, the agent with the broadest range of validated and investigational clinical applications (spasticity, alcohol use disorder, GERD, trigeminal neuralgia, hiccups), and the compound with the longest and most extensive clinical safety database. Its principal limitations are the short half-life requiring multiple daily dosing, the limited and saturable blood-brain barrier penetration, the sedation at higher oral doses, and the clinically significant withdrawal syndrome. These limitations are addressable (intrathecal delivery for the PK limitation; slow titration for sedation; mandatory taper for withdrawal) and have not displaced baclofen from its first-line position in the treatment of spasticity of spinal origin after more than 50 years of clinical use.

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