

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tianeptine

A dibenzothiazepine tricyclic derivative developed by Servier as a serotonin reuptake enhancer, subsequently reclassified as a moderately potent full mu-opioid receptor agonist with downstream effects on AMPA receptor trafficking, hippocampal synaptic plasticity, and stress-induced neuromorphological remodeling.

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ABSTRACT

Tianeptine is an atypical tricyclic antidepressant bearing a dibenzothiazepine nucleus and an aminoheptanoic acid side chain, first synthesized by the Science Union et Cie, Societe Francaise de Recherche Medicale in 1971 and brought to market in France in 1989 by Laboratoires Servier under the brand name Stablon. The compound is approved as an antidepressant in approximately 60 countries, predominantly in Europe, Asia, and Latin America, but is not approved by the United States Food and Drug Administration, Health Canada, or the Australian Therapeutic Goods Administration. Tianeptine was originally classified as a selective serotonin reuptake enhancer on the basis of early microdialysis studies demonstrating increased serotonin clearance from the synaptic cleft, a mechanism diametrically opposite to that of the selective serotonin reuptake inhibitors. This original mechanistic classification was substantially revised by the landmark 2014 report from Gassaway and colleagues, which demonstrated that tianeptine is a moderately potent but highly efficacious and selective full agonist at the mu-opioid receptor (MOR), with K_i of 383 nanomolar and EC_{50} of 194 nanomolar for G-protein activation relative to DAMGO, and negligible affinity at delta-opioid and kappa-opioid receptors [1]. Subsequent studies confirmed that the behavioral antidepressant effects of tianeptine in rodent forced swim test and tail suspension test models are abolished in mu-opioid receptor knockout mice and are blocked by the opioid antagonist naloxone, establishing the MOR as the primary pharmacological target for the antidepressant activity [2].

A second, mechanistically distinct axis of tianeptine pharmacology involves modulation of glutamatergic neurotransmission and synaptic plasticity. Tianeptine stabilizes surface AMPA receptor populations through a calcium/calmodulin-dependent protein kinase II (CaMKII) dependent mechanism that promotes the binding of the AMPA receptor auxiliary subunit stargazin with postsynaptic density protein 95 (PSD-95), thereby reducing AMPA receptor surface diffusion and restoring long-term potentiation in the hippocampus of stressed animals [3, 4]. Tianeptine prevents corticosterone-induced dispersal of AMPA receptors from the postsynaptic density and blocks stress-induced reductions in hippocampal dendritic arborization, spine density, and neurogenesis. These neuroplastic effects are observed at clinically relevant concentrations and are hypothesized to mediate the sustained antidepressant and anxiolytic efficacy that persists beyond the short plasma half-life of the parent compound.

Pharmacokinetics are characterized by near-complete oral bioavailability (approximately 99 percent), rapid absorption with time to peak plasma concentration of approximately one hour, high plasma protein binding (approximately 95 percent), a short elimination half-life for the parent compound of 2.5 to 3 hours necessitating three-times-daily dosing at the standard 12.5 mg dose, and hepatic metabolism predominantly through beta-oxidation (not cytochrome P450 enzymes) to the active metabolite MC5, which retains mu-opioid agonist activity with an EC₅₀ of 545 nanomolar and has a longer elimination half-life of approximately 7.6 hours [5, 6]. The CYP-independent metabolism limits clinically significant drug-drug interactions relative to other antidepressant classes.

Clinical efficacy in major depressive disorder has been established in multiple randomized controlled trials comparing tianeptine with placebo, imipramine, amitriptyline, fluoxetine, paroxetine, and sertraline. A meta-analysis of five randomized controlled trials encompassing 1,348 patients found no significant difference between tianeptine and SSRIs on the Montgomery-Asberg Depression Rating Scale total score or responder rate [7].

Tianeptine demonstrates a tolerability advantage over classical tricyclic antidepressants, producing significantly fewer cardiovascular, anticholinergic, sedative, and weight-gain adverse events, and a tolerability profile broadly comparable to SSRIs with lower rates of sexual dysfunction [8].

The mu-opioid receptor agonism has introduced a substantial abuse liability signal, particularly in the United States where tianeptine has been marketed as an unregulated dietary supplement and sold at gas stations and convenience stores under brand names such as ZaZa and Tianna. At supratherapeutic doses (typically 10- to 100-fold above the clinical dose), tianeptine produces opioid-type euphoria, physical dependence, and a withdrawal syndrome clinically indistinguishable from classical opioid withdrawal [9]. The FDA has issued public warnings, and as of 2026, at least 15 United States states have scheduled or banned tianeptine [10]. Italy became the first European country to classify tianeptine as a controlled substance in 2020. This monograph reviews the chemistry, synthesis, and structural pharmacology of tianeptine; the dual mu-opioid and glutamatergic mechanisms in molecular detail; the comprehensive pharmacokinetic record; the clinical evidence base across depressive, anxious, and comorbid indications; the sourcing, reconstitution, and handling considerations for laboratory work; the stack-interaction profile; the adverse-event and abuse-liability signal; and a comparative

assessment of five antidepressant alternatives against tianeptine
on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Tianeptine.

Marketed names: Stablon (Servier; France, and multiple European, Asian, and Latin American markets), Coaxil (Eastern Europe, Russia, Central Asia), Tatinol (Latin America), Tianeurax (Czech Republic), Salymbra (Portugal).

Development codes: S-1574 (Servier internal designation). The compound is identified in the early patent literature under the corporate name of the Science Union et Cie, Societe Francaise de Recherche Medicale, a subsidiary of Servier [11].

Chemical Abstracts Service registry numbers: 66981-73-5 (free acid), 30123-17-2 (sodium salt). The sodium salt is the pharmaceutical form used in all marketed formulations and in the majority of research-grade preparations. A sulfate salt form (CAS 1224690-84-9) has been developed for sustained-release applications [12].

International Union of Pure and Applied Chemistry name: 7-[(3-chloro-6-methyl-5,5-dioxido-6,11-dihydrodibenzo[c,f][1,2]thiazepine-11-yl)amino]heptanoic acid. The compound is a modified dibenzothiazepine tricyclic with a seven-carbon aminoheptanoic acid side chain attached at the 11-position of the tricyclic nucleus through a secondary amine linkage.

1.2 Structural class and chemistry

Tianeptine belongs to the dibenzothiazepine class of tricyclic compounds. The tricyclic nucleus consists of two benzene rings fused to a central seven-membered thiazepine ring containing a sulfonamide group (S,S-dioxide) and an N-methyl substitution. A chlorine substituent at the 3-position of the aromatic ring and the aminoheptanoic acid side chain at the 11-position are the principal structural features distinguishing tianeptine from other tricyclic antidepressants. The structural resemblance to classical tricyclic antidepressants such as imipramine and amitriptyline is topological rather than pharmacological; the dibenzothiazepine nucleus with its sulfonamide bridge produces a fundamentally different receptor binding profile [13].

Molecular formula: C₂₁H₂₅ClN₂O₄S (free acid); C₂₁H₂₄ClN₂NaO₄S (sodium salt).

Exact mass: 436.12 g/mol (free acid, monoisotopic).

Molecular weight: 436.95 g/mol (free acid); 458.93 g/mol (sodium salt).

Physical properties: White to off-white crystalline powder. The sodium salt is freely soluble in water and in methanol; sparingly soluble in ethanol; practically insoluble in apolar organic solvents. The free acid is less water-soluble. Melting point of the sodium salt is approximately 180 degrees Celsius with decomposition.

Stereochemistry: Tianeptine contains one stereocenter at carbon 11 of the dibenzothiazepine nucleus. The marketed pharmaceutical form is the racemate; both enantiomers contribute to the pharmacological activity, though differential receptor affinities of the individual enantiomers have not been extensively characterized in the published literature. Investigators acquiring research-grade tianeptine should confirm that the material is supplied as the racemate consistent with the pharmaceutical form unless enantiomeric resolution is specifically required for the research application.

1.3 Synthesis

The original synthesis of tianeptine was disclosed in patents filed by the Science Union et Cie in 1970 and 1971 [11]. The synthesis proceeds through construction of the dibenzothiazepine core followed by attachment of the aminoheptanoic acid side chain. In the first stage, nucleophilic substitution of aniline onto an aryl sulfonyl chloride produces the corresponding aryl sulfonamide. Hydrolysis of the ester, chlorination to generate the intermediate acyl chloride, and Friedel-Crafts intramolecular acylation yields the tricyclic ketone intermediate. Reduction of the ketone (typically with sodium borohydride) and chlorination at the benzylic position produces the secondary alkyl chloride of the tianeptine core. In the final stage, nucleophilic substitution using ethyl 7-aminoheptanoate followed by ester hydrolysis affords tianeptine as the free acid, which is converted to the sodium salt by treatment with sodium hydroxide or sodium ethoxide and recrystallization [13]. Modern process-chemistry routes have optimized yield and purity, with pharmaceutical-grade material achieving greater than 99.5 percent chemical purity by HPLC.

2. Abstract

Tianeptine (S-1574) is a dibenzothiazepine tricyclic compound that was developed by Laboratoires Servier as an antidepressant and brought to market in France in 1989 [14]. The compound occupies a unique position in psychopharmacology: originally characterized as a selective serotonin reuptake enhancer (an agent that increases rather than decreases serotonin clearance from the synaptic cleft), tianeptine was subsequently reclassified on the basis of the Gassaway et al. (2014) demonstration that its primary molecular target is the mu-opioid receptor, at which it acts as a moderately potent, highly efficacious, and selective full agonist [1]. This reclassification resolved a long-standing paradox in antidepressant pharmacology: how a compound with opposite effects on serotonin reuptake relative to SSRIs could produce equivalent antidepressant efficacy.

The clinical evidence base for tianeptine in major depressive disorder is substantial. Multiple randomized controlled trials have compared tianeptine with placebo, with classical tricyclic antidepressants (imipramine, amitriptyline), and with SSRIs (fluoxetine, paroxetine, sertraline), establishing non-inferiority to all active comparators on standard depression rating scales [7, 8, 15]. A meta-analysis of five randomized controlled trials against SSRIs encompassing 1,348 patients found no significant difference on Montgomery-Asberg Depression Rating Scale (MADRS) total score or responder rate [7]. The tolerability profile favors tianeptine over classical tricyclics (fewer cardiovascular, anticholinergic, and sedative adverse events) and is broadly comparable to SSRIs with the notable advantage of lower sexual dysfunction rates [8].

A second axis of pharmacological activity involves modulation of glutamatergic neurotransmission and synaptic plasticity. Tianeptine stabilizes surface AMPA receptor populations through CaMKII-dependent mechanisms, prevents stress-induced dispersal of AMPA receptors from the postsynaptic density, blocks corticosterone-induced impairment of hippocampal long-term potentiation, and reverses stress-induced reductions in hippocampal dendritic arborization and spine density [3, 4, 16]. These neuroplastic effects provide a mechanistic substrate for the sustained antidepressant activity and for the demonstrated anxiolytic and neuroprotective properties.

The mu-opioid agonism, however, confers a significant abuse liability signal. At supratherapeutic doses, tianeptine produces opioid-type euphoria, reinforcement, physical dependence, and a withdrawal syndrome indistinguishable from classical opioid withdrawal [9]. This abuse potential has driven regulatory action in multiple jurisdictions and has prevented approval in the United States, Canada, and Australia.

3. Discovery and Development History

3.1 Origin

Tianeptine was first synthesized in 1971 by chemists at the Science Union et Cie, Societe Francaise de Recherche Medicale, a research subsidiary of Laboratoires Servier, as part of a structural exploration of dibenzothiazepine derivatives as potential psychotropic agents [11]. The compound was designed as a structural analog of the recently discovered tricyclic antidepressants but with a modified central ring (thiazepine with sulfonamide bridge rather than the dihydroazepine of imipramine or the cycloheptadiene of amitriptyline) and a long aminoheptanoic acid side chain intended to modulate pharmacokinetic and receptor-binding properties.

3.2 Serotonin reuptake enhancement hypothesis

Early pharmacological characterization in the late 1970s and 1980s positioned tianeptine as a selective serotonin reuptake enhancer, an agent that increases the rate of serotonin clearance from the synaptic cleft. In vivo microdialysis studies in rat hippocampus demonstrated that acute and chronic tianeptine administration decreased extracellular serotonin concentrations, opposite to the effect of SSRIs and tricyclic antidepressants [17]. This finding was paradoxical within the monoamine hypothesis of depression, which predicted that increasing (not decreasing) synaptic serotonin should produce antidepressant effects. Servier advanced the compound through clinical development on the basis of empirical efficacy data despite the mechanistic paradox, and the serotonin reuptake enhancement mechanism was the primary descriptor used in marketing and in the clinical literature for approximately 25 years [14].

3.3 Clinical development and registration

Clinical trials in major depressive disorder began in the early 1980s. Tianeptine received its first marketing authorization in France in 1989 under the brand name Stablon at a dose of 12.5 mg three times daily [14]. Subsequent approvals were obtained throughout continental Europe (including Portugal, Bulgaria, Romania, Slovakia, Poland, Hungary, Czech Republic, Austria, Latvia, Estonia, Lithuania,

Slovenia, Malta, and Luxembourg), in Russia and former Soviet states (as Coaxil), in multiple Latin American markets (as Stablon and Tatinol), and in several Asian markets including Singapore [18]. The compound has not been approved in the United States, the United Kingdom, Canada, Australia, or New Zealand.

3.4 Mechanistic reclassification

The serotonin reuptake enhancement hypothesis was progressively weakened by findings that the serotonin effects were modest, inconsistently replicated across assay systems, and insufficient to explain the full pharmacological profile. Beginning in the mid-2000s, the McEwen laboratory and collaborators demonstrated that tianeptine's principal neurobiological effects involved modulation of glutamatergic neurotransmission and synaptic plasticity rather than serotonergic reuptake [16, 19].

The definitive mechanistic reclassification came with the 2014 publication by Gassaway, Rief, Khalili-Araghi, and colleagues, who used an unbiased receptor screening approach to demonstrate that tianeptine is a full agonist at the mu-opioid receptor with K_i of 383 nanomolar and EC_{50} of 194 nanomolar, with negligible affinity at delta-opioid and kappa-opioid receptors and at more than 70 other receptor and transporter targets tested [1]. The Samuels laboratory subsequently confirmed that the behavioral antidepressant effects of tianeptine (forced swim test, tail suspension test) are abolished in mu-opioid receptor knockout mice and blocked by naloxone pretreatment [2]. Further work demonstrated that MOR activation on hippocampal GABAergic interneurons is critical for the antidepressant effects, providing a circuit-level mechanism linking MOR agonism to hippocampal plasticity [20].

3.5 Abuse liability recognition and regulatory response

Reports of tianeptine abuse and dependence began appearing in the clinical literature in the early 2000s, principally from France and Eastern European countries where the compound was widely prescribed [21]. In the United States, tianeptine became available as an unregulated dietary supplement and was marketed in convenience stores and gas stations under brand names such as ZaZa, Tianna, and TD Red, typically at doses far exceeding the clinical 12.5 mg [9]. The FDA issued consumer warnings designating tianeptine products as unapproved new drugs and identifying the abuse pattern as "gas station heroin" [22]. As of 2026, at least 15 United States states have classified tianeptine as a controlled substance (Schedule I

or II) or have banned its sale outright [10]. Italy became the first European Union member state to classify tianeptine as a controlled substance (Class I) in March 2020 [18]. Singapore restricted tianeptine prescribing to psychiatrists in 2001 [18].

4. Mechanism of Action

Tianeptine is a multi-mechanism agent whose pharmacological profile encompasses mu-opioid receptor agonism, glutamatergic synaptic plasticity modulation, and downstream neurotrophic and anti-inflammatory effects. The original serotonin reuptake enhancement classification has been superseded by the opioid and glutamatergic mechanisms described below.

4.1 Mu-opioid receptor agonism

The mu-opioid receptor (MOR) is a G-protein-coupled receptor of the rhodopsin family, coupled primarily to inhibitory Gi/Go proteins. Activation produces inhibition of adenylyl cyclase, reduction of cyclic AMP, activation of inwardly rectifying potassium channels (GIRK), inhibition of voltage-gated calcium channels, and modulation of mitogen-activated protein kinase (MAPK) pathways. The MOR is the molecular target of morphine, fentanyl, and endogenous opioid peptides (beta-endorphin, endomorphins) and mediates analgesia, reward, respiratory depression, and physical dependence [1].

Tianeptine binds the MOR with a K_i of 383 nanomolar (plus or minus 183 nanomolar) determined by radioligand displacement of [3H]-DAMGO in human MOR-expressing HEK293 cells [1]. Functionally, tianeptine is a full agonist with an E_{max} exceeding 100 percent relative to the reference full agonist DAMGO in [35S]-GTPgammaS assays, with EC_{50} values of 194 nanomolar (human MOR) and 641 nanomolar (mouse MOR). Selectivity for MOR over delta-opioid receptor (DOR) and kappa-opioid receptor (KOR) is greater than 50-fold; tianeptine does not produce appreciable activation at DOR or KOR at concentrations up to 10 micromolar [1].

The downstream consequences of MOR activation relevant to antidepressant activity include: decreased protein kinase A (PKA) activity in hippocampal neurons, resulting in decreased phosphorylation of NMDA receptor subunits and reduced NMDA receptor-mediated excitotoxicity; disinhibition of CA1 hippocampal pyramidal neurons through MOR-mediated suppression of GABAergic interneuron firing; and increased dopamine release in the nucleus accumbens through MOR activation in the ventral tegmental area [1, 20]. The hippocampal GABAergic interneuron mechanism, demonstrated by Bhatt et al. (2021) using conditional MOR knockout

mice, is particularly significant: selective deletion of MOR from hippocampal GABAergic interneurons abolished the antidepressant effects of tianeptine while preserving the analgesic effects, establishing a circuit-specific dissociation between the antidepressant and analgesic/rewarding properties [20].

4.2 Glutamatergic modulation and synaptic plasticity

Tianeptine does not have appreciable direct affinity (K_i greater than 10 micromolar) for NMDA, AMPA, or kainate ionotropic glutamate receptors, nor agonist or antagonist activity at metabotropic glutamate receptors [1]. The glutamatergic effects are therefore indirect, mediated through downstream signaling cascades initiated by MOR activation and through direct effects on AMPA receptor trafficking and surface dynamics.

The AMPA receptor modulation has been characterized in detail by the Bhatt laboratory and collaborators [3, 4]. Tianeptine stabilizes surface AMPA receptor (AMPA) populations by reducing their lateral diffusion within the postsynaptic membrane through a CaMKII-dependent mechanism. Specifically, tianeptine activates CaMKII, which phosphorylates the AMPAR auxiliary subunit stargazin (TARP gamma-2), promoting its binding to PSD-95, the principal postsynaptic scaffolding protein. This stargazin-PSD-95 interaction immobilizes AMPARs at the synapse, increasing synaptic AMPAR content and potentiating excitatory postsynaptic currents [4].

In stress models, corticosterone and chronic unpredictable stress produce dispersal of AMPARs from the postsynaptic density, impaired long-term potentiation (LTP), and reduced dendritic spine density in hippocampal CA1 and dentate gyrus neurons. Tianeptine prevents these stress-induced changes: it blocks corticosterone-induced AMPAR surface dispersal, restores LTP in hippocampal slices from stressed animals, and normalizes dendritic morphology [3, 16]. The AMPAR phosphorylation involves activation of p38, p42/44 MAPK, and JNK signaling pathways, and PKA-dependent phosphorylation of the GluA1 subunit at Ser845 [23].

4.3 Neurotrophic effects

Tianeptine administration produces increased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, increased hippocampal neurogenesis in the dentate gyrus, reversal of stress-induced hippocampal volume reduction

(demonstrated by magnetic resonance imaging in rodent models), and normalization of hypothalamic-pituitary-adrenal axis hyperactivation in chronically stressed animals [16, 19]. These effects are consistent with a neurotrophic and neurorestorative mechanism that extends beyond acute receptor-level pharmacology and may account for the sustained clinical efficacy observed with chronic dosing.

4.4 Serotonin reuptake effects

The original serotonin reuptake enhancement observation, while consistently replicated in in vivo microdialysis studies, is now understood to be a secondary consequence of MOR activation rather than a primary pharmacological mechanism. MOR-mediated modulation of serotonergic neuron firing rates in the dorsal raphe nucleus produces downstream effects on serotonin release and reuptake that are consistent with the microdialysis observations but are not the causal mechanism of the antidepressant effect [1]. Tianeptine does not bind the serotonin transporter (SERT) at clinically relevant concentrations; the apparent K_i at SERT is greater than 10 micromolar [1].

4.5 Composite pharmacology at clinical concentrations

At the standard clinical dose of 12.5 mg three times daily, peak plasma concentrations of tianeptine reach approximately 500 to 900 nanograms per milliliter (approximately 1.1 to 2.1 micromolar), with trough concentrations at 8 hours of approximately 50 to 100 nanograms per milliliter (approximately 0.1 to 0.2 micromolar) [5]. Given the K_i of 383 nanomolar and approximately 95 percent plasma protein binding, free plasma concentrations at peak are approximately 55 to 105 nanomolar, providing partial MOR occupancy. The active metabolite MC5, which reaches steady-state over approximately one week with a half-life of 7.6 hours, contributes additional sustained MOR activation at lower potency (EC_{50} of 545 nanomolar) [6]. The composite parent plus metabolite MOR engagement therefore provides intermittent near-full occupancy at peak and sustained partial occupancy at trough, a temporal pattern that may be relevant to the relatively low abuse potential at therapeutic doses compared to the continuous high-occupancy pattern produced by classical opioid agonists.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Tianeptine sodium is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is approximately 99 percent, reflecting minimal first-pass hepatic metabolism [5]. Time to peak plasma concentration (T_{max}) is approximately 1 to 1.5 hours in fasted subjects. Food delays absorption modestly (T_{max} extended to approximately 2 hours) without significantly affecting overall bioavailability (AUC). Maximum plasma concentration (C_{max}) after a single 12.5 mg oral dose in healthy adults is approximately 500 to 900 nanograms per milliliter [5].

5.2 Distribution

The apparent volume of distribution is low, approximately 0.5 to 0.8 liters per kilogram, consistent with predominant distribution in the vascular and extracellular fluid compartments with limited tissue partitioning [5]. Plasma protein binding is approximately 95 percent, predominantly to albumin and alpha-1-acid glycoprotein. The compound crosses the blood-brain barrier; central nervous system penetration has been inferred from pharmacological effects and from the demonstrated MOR occupancy and AMPAR modulation in hippocampal tissue. Specific positron emission tomography studies of central receptor occupancy have not been published for tianeptine.

5.3 Metabolism

Tianeptine is metabolized predominantly in the liver through beta-oxidation of the aminoheptanoic acid side chain, a metabolic pathway that is independent of the cytochrome P450 enzyme system [5, 6]. This CYP-independence is pharmacokinetically significant: it substantially reduces the potential for drug-drug interactions with the large number of psychotropic and non-psychotropic agents metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

The principal metabolic pathway involves sequential two-carbon shortening of the heptanoic acid side chain through beta-oxidation, analogous to fatty acid catabolism. The primary active metabolite is MC5, the pentanoic acid derivative (5-carbon side chain), produced by removal of one two-carbon unit. Further beta-oxidation produces MC3, the propionic acid derivative (3-carbon side chain), which has reduced pharmacological activity [6].

MC5 retains mu-opioid agonist activity with EC₅₀ of 545 nanomolar (compared to 194 nanomolar for the parent compound) but does not activate delta-opioid receptors [6]. The MC5 metabolite has a longer elimination half-life than the parent compound (approximately 7.6 hours versus 2.5 hours), and reaches steady-state concentrations over approximately one week of daily dosing. In elderly subjects, the MC5 half-life extends to approximately 11.9 hours [24].

5.4 Elimination

The elimination half-life of tianeptine in healthy adults is short, approximately 2.5 to 3 hours, necessitating three-times-daily dosing to maintain therapeutic plasma concentrations [5]. Renal excretion accounts for the majority of eliminated drug, predominantly as metabolites (MC5, MC3, and further oxidized products); less than 3 percent of an administered dose is excreted unchanged in urine [5]. Total body clearance is approximately 240 milliliters per minute.

In elderly subjects (over 70 years of age), the elimination half-life of tianeptine is prolonged to approximately 3.5 to 4 hours, and AUC is increased by approximately 30 to 50 percent, supporting the dose reduction to 12.5 mg twice daily recommended in some prescribing labels [24]. Renal impairment (creatinine clearance less than 19 milliliters per minute) prolongs the half-life of MC5 substantially and warrants dose adjustment. Hepatic impairment has not been extensively studied, but given the beta-oxidation metabolic pathway, severe hepatic insufficiency may impair clearance.

5.5 Routes of administration

The only registered route of administration is oral. Tianeptine sodium is supplied as 12.5 mg immediate-release tablets for three-times-daily dosing (Stablon, Coaxil). A modified-release formulation using the sulfate salt has been developed for once-daily dosing; clinical data on the modified-release form are limited [12].

Intravenous, intramuscular, and subcutaneous routes have not been registered and are not used in clinical practice. Research-grade tianeptine has been administered intraperitoneally in rodent studies at doses of 10 to 30 mg/kg.

5.6 Special populations

Elderly: Pharmacokinetic studies in subjects over 70 years of age demonstrate increased exposure (approximately 30 to 50 percent higher AUC) and prolonged MC5 elimination. Dose reduction to 12.5 mg twice daily is recommended [24].

Renal impairment: Moderate to severe renal impairment prolongs MC5 elimination. Dose adjustment is recommended for creatinine clearance below 19 milliliters per minute.

Hepatic impairment: Limited data. The beta-oxidation metabolic pathway may be less affected by hepatic dysfunction than CYP-mediated metabolism, but caution is appropriate.

Pediatric: Tianeptine is not approved for use in children or adolescents. Pediatric pharmacokinetic data are not available.

Alcohol co-administration: A pharmacokinetic interaction study in healthy volunteers demonstrated that alcohol co-administration does not significantly alter tianeptine pharmacokinetics [25].

6. Preclinical Pharmacology

6.1 Antidepressant behavioral models

Tianeptine has been evaluated across the principal rodent behavioral paradigms used to screen for antidepressant activity. In the forced swim test, tianeptine at 10 mg/kg intraperitoneal reduces immobility time to a degree comparable to imipramine and fluoxetine at their respective effective doses [2]. In the tail suspension test, tianeptine produces similar immobility reductions. Critically, Samuels et al. (2017) demonstrated that these behavioral effects are entirely dependent on MOR signaling: in mu-opioid receptor knockout mice, tianeptine failed to reduce immobility in either test, and the opioid antagonist naloxone (1 mg/kg intraperitoneal) pretreatment fully blocked the behavioral effect in wild-type mice [2].

6.2 Chronic stress models

In chronic unpredictable stress (CUS) and chronic social defeat stress (CSDS) models, tianeptine reverses anhedonia (measured by sucrose preference), social avoidance, and anxiety-like behavior in the elevated plus maze. The reversal of stress-induced behavioral deficits is accompanied by normalization of hippocampal dendritic morphology and restoration of BDNF expression [16, 19].

6.3 Synaptic plasticity

Electrophysiological studies in hippocampal slices demonstrate that tianeptine facilitates long-term potentiation (LTP) in the CA1 Schaffer collateral pathway and in the dentate gyrus perforant path. Acute stress impairs LTP in these circuits; tianeptine pretreatment prevents the stress-induced LTP deficit and, when administered after stress, partially restores LTP magnitude [3, 4]. The mechanism involves stabilization of surface AMPAR populations through CaMKII-stargazin-PSD-95 signaling as described in Section 4.2.

6.4 Hippocampal neuromorphology

Chronic tianeptine administration (21 days, 10 mg/kg intraperitoneal in rats) prevents stress-induced apical dendritic atrophy in CA3 hippocampal pyramidal neurons, a structural change that is robustly produced by chronic restraint stress and that correlates with hippocampal-dependent memory impairment [19]. Tianeptine also prevents stress-induced reductions in hippocampal volume (measured by MRI) and in dentate gyrus cell proliferation [26].

6.5 Opioid-related pharmacology

Tianeptine produces dose-dependent antinociception in the hot plate and tail flick assays, blocked by naloxone pretreatment [27]. Chronic administration at doses exceeding the anxiolytic/antidepressant range (30 mg/kg daily for 14 days) produces tolerance to the analgesic effect and physical dependence, with naloxone-precipitated withdrawal signs including jumping, wet-dog shakes, diarrhea, and piloerection [27]. These preclinical dependence findings are consistent with the clinical reports of opioid-type withdrawal in human users at supratherapeutic doses.

7. Clinical Evidence Base

7.1 Major depressive disorder: placebo-controlled trials

The antidepressant efficacy of tianeptine has been established in randomized, double-blind, placebo-controlled trials in patients meeting diagnostic criteria for major depressive disorder or depressed bipolar disorder. Two pivotal placebo-controlled trials (Costa e Silva 1997, Guelfi et al. 1989) demonstrated statistically significant superiority of tianeptine 12.5 mg three times daily over placebo on the MADRS and Hamilton Depression Rating Scale (HDRS) over 6 to 8 weeks of treatment [15, 28]. Response rates (defined as 50 percent or greater reduction in MADRS score) were approximately 55 to 65 percent on tianeptine versus 30 to 40 percent on placebo.

7.2 Major depressive disorder: active comparator trials

Versus imipramine: Multiple trials (Guelfi et al. 1989, Luo et al. 1996, Cassano et al. 1996) compared tianeptine 37.5 mg daily with imipramine 150 mg daily over 4 to 6 weeks. Efficacy on MADRS and HDRS was equivalent. Tolerability strongly favored tianeptine, with significantly lower rates of anticholinergic effects (dry mouth, constipation, urinary retention), cardiovascular effects (orthostatic hypotension, tachycardia, conduction abnormalities), sedation, and weight gain [15, 29].

Versus amitriptyline: Dalery et al. (1997) compared tianeptine with amitriptyline in a 6-week randomized double-blind trial in depressed alcoholic patients, demonstrating equivalent antidepressant efficacy with a markedly better tolerability profile for tianeptine, and showed additional benefit in reducing alcohol consumption [30].

Versus fluoxetine: Two randomized controlled trials (Leinonen et al. 1999, Novotny and Faltus 2002) compared tianeptine with fluoxetine 20 mg daily. Final MADRS scores were 15.7 and 15.8 for tianeptine and fluoxetine respectively, with 58 percent and 56 percent MADRS responder rates. Tianeptine produced fewer reports of sexual dysfunction and insomnia [31].

Versus paroxetine: Waintraub et al. (2002) conducted a 3-month randomized controlled trial comparing tianeptine 37.5 mg daily with paroxetine 20 mg daily in 277 patients with major depression. Efficacy was comparable on all primary and secondary endpoints. Discontinuation rates for adverse events were lower with tianeptine [32].

Versus sertraline: One randomized controlled trial compared tianeptine with sertraline 50 mg daily over 6 weeks, finding equivalent efficacy and comparable tolerability [7].

7.3 Meta-analysis: tianeptine versus SSRIs

Kasper and Olie (2002) published a meta-analysis of five randomized controlled trials comparing tianeptine with SSRIs (two versus fluoxetine, two versus paroxetine, one versus sertraline) encompassing 1,348 patients (667 tianeptine, 681 SSRI). Neither MADRS total score nor MADRS responder rate showed any significant difference between the two treatment groups, establishing statistical non-inferiority of tianeptine to the SSRI class [7].

7.4 Anxiety and comorbid depression-anxiety

Tianeptine has demonstrated anxiolytic activity in clinical trials conducted in patients with comorbid depression and anxiety. The anxiolytic effect, measured by the Hamilton Anxiety Rating Scale (HAM-A) and by anxiety subscales of the MADRS, is present from the first week of treatment and is of comparable magnitude to the anxiolytic effect of fluoxetine 20 mg [8]. A separate analysis established that tianeptine 37.5 mg daily has equivalent anxiolytic activity to fluoxetine 20 mg daily on the HAM-A [8].

7.5 Post-traumatic stress disorder

Limited clinical evidence supports tianeptine in post-traumatic stress disorder (PTSD). Open-label and small controlled studies have reported reductions in PTSD symptom scores, consistent with the compound's effects on hippocampal plasticity and stress-related neurocircuitry. The evidence base is insufficient for regulatory registration in this indication.

7.6 Asthma and respiratory illness comorbid with depression

A distinctive feature of the tianeptine clinical evidence base is the demonstration of antidepressant efficacy without the bronchospastic risk associated with some serotonergic antidepressants. The compound has been studied in patients with asthma and comorbid depression, where it produced antidepressant effects without worsening respiratory function [8]. This observation is consistent with the absence of significant serotonergic receptor binding and the predominantly opioid and glutamatergic mechanism.

7.7 Elderly depression

Tianeptine has been specifically studied in elderly patients with major depression. Efficacy is maintained in the elderly population at the reduced dose of 12.5 mg twice daily, with tolerability comparable to the younger adult population [24]. The absence of significant anticholinergic, cardiovascular, and sedative adverse events is a practical advantage over classical tricyclic antidepressants in the elderly.

8. Sourcing and Quality Verification

Pharmaceutical-grade tianeptine (Stablon, Coaxil) is the highest quality source for research applications. The pharmaceutical-grade material is supplied as 12.5 mg immediate-release coated tablets in the marketed formulations. Pharmaceutical sourcing is feasible in jurisdictions where the compound is registered (France, Portugal, Romania, Bulgaria, Poland, Hungary, Czech Republic, Russia, and multiple Latin American and Asian markets) but may be restricted in jurisdictions that have scheduled the compound.

Research-grade tianeptine sodium is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Tocris, MedChemExpress, Santa Cruz Biotechnology, Focus Biomolecules, and others) at greater than 98 percent purity by HPLC. Supply is available in milligram to gram quantities as the sodium salt. Research-grade tianeptine free acid is also available but less common. The sulfate salt is available from specialized suppliers [12].

The regulatory environment is evolving rapidly. In the United States, tianeptine is not a federally scheduled controlled substance as of 2026, but at least 15 states have enacted scheduling or sales bans [10]. Investigators should confirm the legal status in their jurisdiction before procurement. In Italy, tianeptine is a Class I controlled substance [18]. Investigators in all jurisdictions should maintain chain-of-custody documentation and institutional approval for work with this compound given its recognized abuse liability.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (437.12 for the protonated free acid $[M+H]^+$, or 459.10 for the sodium salt $[M+Na]^+$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Given the abuse-diversion risk associated with tianeptine, investigators should exercise particular diligence in inventory control and secure storage.

9. Reconstitution and Handling

Tianeptine sodium is freely soluble in water at room temperature. For in vitro research applications, the compound is typically supplied as a crystalline powder and reconstituted as stock solutions at 10 to 100 millimolar in water, phosphate-buffered saline, or dimethyl sulfoxide (DMSO) for applications requiring higher concentrations. DMSO stock solutions at 100 millimolar are stable at minus 20 degrees Celsius for at least 6 months.

Aqueous stock solutions should be prepared fresh or stored at 2 to 8 degrees Celsius for no more than 7 to 14 days. The compound is stable in aqueous solution at physiological pH (7.2 to 7.6) and at refrigerated temperatures for this period. Repeated freeze-thaw cycles should be avoided; aliquoting into single-use volumes is recommended.

The solid powder should be stored at minus 20 degrees Celsius in a sealed, desiccated container protected from light. Under these conditions, the powder is stable for at least 2 years with no measurable degradation.

For in vivo rodent studies, tianeptine is typically dissolved in normal saline (0.9 percent sodium chloride) at concentrations of 1 to 3 mg/milliliter for intraperitoneal injection. The solution should be prepared fresh on the day of administration or within 24 hours if stored refrigerated.

Investigators should handle tianeptine with appropriate precautions for a mu-opioid receptor agonist. While the compound has low potency relative to fentanyl and its analogs (approximately 1000-fold lower MOR affinity), accidental ingestion of research-grade material could produce opioid effects. Standard laboratory personal protective equipment (gloves, lab coat, eye protection) is appropriate.

10. Stack Interaction Considerations

Tianeptine's CYP-independent metabolism through beta-oxidation limits pharmacokinetic drug-drug interactions relative to other antidepressant classes. However, pharmacodynamic interactions and specific pharmacokinetic considerations apply.

Monoamine oxidase inhibitors (MAOIs): Concurrent use of tianeptine with MAOIs (phenelzine, tranylcypromine, selegiline, moclobemide) is contraindicated. Although the pharmacological mechanism of this interaction has not been fully elucidated (tianeptine does not strongly inhibit serotonin reuptake at clinical concentrations), the prescribing label maintains a standard 14-day washout period between MAOI and tianeptine administration [14].

Opioid agonists and antagonists: Concurrent use with other mu-opioid agonists (morphine, oxycodone, hydrocodone, tramadol, methadone, buprenorphine) produces additive MOR activation, increasing the risk of respiratory depression, sedation, and physical dependence. Opioid antagonists (naloxone, naltrexone) will block the mu-opioid component of tianeptine's pharmacological activity, potentially reducing antidepressant efficacy; naltrexone co-administration has not been studied in a clinical antidepressant context but would be predicted to attenuate or abolish the antidepressant effect based on the MOR-dependence demonstrated in knockout studies [2].

Benzodiazepines and sedatives: Additive central nervous system depression may occur with concurrent benzodiazepines, barbiturates, or other sedative-hypnotics. The interaction is pharmacodynamic and dose-dependent.

SSRIs and SNRIs: No significant pharmacokinetic interaction is expected given tianeptine's CYP-independent metabolism. The pharmacodynamic interaction is complex: tianeptine does not strongly engage serotonergic targets, but concurrent serotonergic and opioidergic modulation has not been extensively studied in controlled clinical trials. Some prescribing labels recommend caution with concurrent serotonergic agents.

Ethanol: Pharmacokinetic studies demonstrate no significant interaction between ethanol and tianeptine at the pharmacokinetic level [25]. However, pharmacodynamic potentiation of sedation and psychomotor impairment is expected with

concurrent ethanol use.

QT-prolonging agents: Tianeptine has not been associated with clinically significant QT interval prolongation in postmarketing surveillance. No specific QT-related drug interaction warnings are included in current prescribing labels.

Anesthetic agents: Tianeptine should be discontinued prior to elective surgery requiring general anesthesia, given the potential for additive central nervous system and respiratory depression with opioid-based anesthetic regimens. The prescribing label recommends discontinuation 24 to 48 hours prior to planned general anesthesia [14].

Cholinergic agents: No significant interaction expected. Tianeptine does not have appreciable anticholinergic activity, distinguishing it from classical tricyclic antidepressants.

11. Adverse Events and Safety

11.1 Common adverse events at therapeutic doses

The principal adverse events at the registered dose of 12.5 mg three times daily are:

- Nausea (8 to 12 percent; the most common adverse event, typically transient and decreasing with continued treatment)
- Constipation (5 to 8 percent)
- Abdominal pain (4 to 7 percent)
- Headache (5 to 10 percent)
- Dizziness (3 to 6 percent)
- Change in dreaming and insomnia (3 to 5 percent)
- Dry mouth (2 to 4 percent; substantially lower than classical tricyclic antidepressants)

These adverse-event rates are broadly comparable to SSRIs. Tianeptine produces significantly fewer anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision) than imipramine and amitriptyline. Weight gain is minimal and comparable to placebo, distinguishing tianeptine from the weight-gain-associated antidepressants (mirtazapine, amitriptyline, paroxetine). Sexual dysfunction is reported at rates substantially lower than SSRIs, a clinically meaningful tolerability advantage [8, 32].

11.2 Cardiovascular safety

Unlike classical tricyclic antidepressants, tianeptine does not significantly affect cardiac conduction (QRS duration, QT interval, PR interval) or hemodynamic parameters (blood pressure, heart rate) at therapeutic doses [15]. The compound does not produce the sodium channel blockade and alpha-1 adrenergic antagonism responsible for the cardiovascular toxicity of imipramine and amitriptyline. This cardiovascular safety profile is a significant advantage in elderly patients and in patients with cardiovascular comorbidity.

11.3 Abuse liability and dependence

The mu-opioid receptor agonism confers a dose-dependent abuse liability that is the most significant safety concern associated with tianeptine. At therapeutic doses (37.5 mg daily), the abuse potential appears low: clinical trials and long-term follow-up studies have not identified significant rates of misuse, dose escalation, or physical dependence [8]. However, at supratherapeutic doses (typically 125 mg to over 2,000 mg daily, representing 3- to 50-fold or greater dose escalation), tianeptine produces classical opioid-type effects including euphoria, anxiolysis, analgesic warmth, and reinforcement [9, 21].

Physical dependence develops with chronic supratherapeutic dosing. Withdrawal symptoms upon abrupt discontinuation are indistinguishable from classical opioid withdrawal and include: muscle pain, nausea, vomiting, diarrhea, sweating, piloerection, insomnia, anxiety, irritability, tachycardia, and intense craving [9]. The withdrawal timeline is consistent with the short half-life: onset within 4 to 8 hours of the last dose, peak intensity at 24 to 48 hours, and gradual resolution over 5 to 10 days. Treatment of tianeptine withdrawal follows established opioid withdrawal management protocols, including buprenorphine or methadone tapering in severe cases [9].

Case reports of tianeptine abuse and fatal overdose have been reported in France, Eastern Europe, Russia, and the United States [21, 22]. The lethal dose in humans has not been precisely established; fatal outcomes have been reported at estimated ingested doses of 2,000 mg or greater, typically in combination with other central nervous system depressants.

11.4 Hepatic effects

Rare cases of hepatotoxicity (elevated transaminases, cholestatic hepatitis) have been reported in postmarketing surveillance. The incidence is low, and the hepatotoxicity signal is not considered a clinically significant limitation at therapeutic doses.

11.5 Overdose

Tianeptine in overdose at up to 10-fold the therapeutic dose (approximately 375 mg) produces nausea, vomiting, drowsiness, and mild respiratory depression; outcomes are generally favorable with supportive care. At higher overdose levels

(greater than 1,000 mg), particularly in combination with other CNS depressants, respiratory depression, coma, and death may occur. Naloxone is effective as an antidote for tianeptine-induced respiratory depression, consistent with the MOR-dependent mechanism [9].

11.6 Pregnancy and lactation

Animal reproductive toxicity studies have not demonstrated teratogenicity at doses up to 16-fold the human therapeutic dose. Human pregnancy data are limited. The compound is not recommended during pregnancy unless clearly indicated. Tianeptine is excreted in human milk; use during lactation is discouraged [14].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five antidepressant alternatives against tianeptine, 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 represent the principal mechanistic classes relevant to tianeptine's positioning: classical tricyclic antidepressants (imipramine), SSRIs (fluoxetine), novel glutamatergic agents (esketamine), multimodal serotonergic agents (vortioxetine), and atypical antidepressants with opioidergic activity (buprenorphine/samidorphan).

12.1 Imipramine

Mechanism: Non-selective monoamine reuptake inhibitor (serotonin and norepinephrine) with significant anticholinergic, antihistaminic, and alpha-1 adrenergic antagonist activity. Sodium channel blockade at supratherapeutic concentrations produces the principal cardiovascular toxicity.

Development trajectory: Imipramine was the first tricyclic antidepressant, introduced by Geigy (now Novartis) in 1957. It remains one of the most extensively studied antidepressants in history, with thousands of clinical trials spanning six decades.

Novelty: Very low. Imipramine is the prototypical tricyclic antidepressant and the historical reference compound for the class.

Effect size: Large. Meta-analyses consistently rank imipramine among the most efficacious antidepressants, with effect sizes (Cohen's d) of approximately 0.5 to 0.7 versus placebo on the HDRS [33]. In head-to-head trials, tianeptine produces comparable antidepressant efficacy to imipramine at registered doses [15, 29].

Promising potential: Low for new indications. The compound is well established but is progressively displaced by better-tolerated alternatives. Generic availability is universal.

Side-effect profile: Substantially less favorable than tianeptine. Imipramine produces dose-dependent anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision), cardiovascular effects (orthostatic hypotension, tachycardia, QRS and QT prolongation), sedation, weight gain, and sexual dysfunction. The cardiovascular toxicity produces a narrow therapeutic index and makes imipramine dangerous in overdose. Tianeptine is substantially better tolerated on all of these parameters [15].

Overall validation: Very high. The compound has the most extensive clinical evidence base of any antidepressant. However, its tolerability profile limits contemporary use.

Comparison to tianeptine: Tianeptine produces equivalent antidepressant efficacy with a markedly superior tolerability profile. The principal advantage of imipramine is its very extensive evidence base and its efficacy in treatment-resistant depression. The principal advantage of tianeptine is its cardiovascular safety, absence of anticholinergic burden, and weight neutrality.

12.2 Fluoxetine

Mechanism: Selective serotonin reuptake inhibitor (SSRI). Binds the serotonin transporter (SERT) with high affinity and selectivity over norepinephrine and dopamine transporters.

Development trajectory: Introduced by Eli Lilly in 1987 as Prozac, the first SSRI to achieve widespread clinical use. The compound transformed the antidepressant market and remains one of the most prescribed antidepressants globally.

Novelty: Low. SSRIs are the standard first-line antidepressant class.

Effect size: Moderate. Meta-analyses place fluoxetine effect sizes at approximately 0.3 to 0.5 versus placebo on the HDRS, slightly lower than imipramine [33]. In head-to-head trials, tianeptine produces equivalent efficacy to fluoxetine, with MADRS responder rates of 58 percent (tianeptine) versus 56 percent (fluoxetine) [31].

Promising potential: Moderate. Fluoxetine continues to be widely prescribed and studied, but the mechanism is well established and offers limited novelty for new applications.

Side-effect profile: Broadly comparable to tianeptine overall, with important differences. Fluoxetine produces higher rates of sexual dysfunction (decreased libido, anorgasmia, delayed ejaculation), insomnia, and activation-type anxiety in the first weeks of treatment. Tianeptine produces lower rates of sexual dysfunction and insomnia but modestly higher rates of gastrointestinal symptoms [8, 31]. Weight effects are similar (both are weight-neutral or associated with modest weight loss).

Overall validation: Very high. One of the most extensively studied antidepressants with a massive clinical and epidemiological evidence base.

Comparison to tianeptine: The two compounds produce equivalent antidepressant efficacy. Tianeptine's advantages are lower sexual dysfunction and a distinct mechanism of action that may benefit patients who do not respond to SSRIs. Fluoxetine's advantages are the very extensive evidence base, global availability, regulatory approval in the United States and essentially all other major markets, and the absence of abuse liability concerns.

12.3 Esketamine (Spravato)

Mechanism: Non-competitive antagonist at the N-methyl-D-aspartate (NMDA) glutamate receptor. The (S)-enantiomer of ketamine, with approximately 3- to 4-fold higher affinity for the NMDA receptor than the (R)-enantiomer. Downstream effects include rapid activation of AMPA receptor-mediated signaling, increased BDNF release, and activation of mTOR-dependent synaptogenesis.

Development trajectory: Developed by Janssen (Johnson and Johnson) and approved by the FDA in 2019 as Spravato (intranasal esketamine) for treatment-resistant depression and, subsequently, for major depressive disorder with acute suicidal ideation or behavior. The approval was based on Phase 3 trials demonstrating rapid-onset antidepressant effects (within hours to days) in treatment-resistant patients.

Novelty: High. The glutamatergic/NMDA antagonist mechanism represents a fundamentally different approach to antidepressant pharmacology and has been the most significant advance in the field since the introduction of SSRIs.

Effect size: Large in the acute setting. Treatment-resistant depression trials demonstrated approximately 4-point separation from placebo on the MADRS at 24 hours post-dose [34]. However, effect durability requires repeated intranasal ad-

ministration under clinical supervision, and long-term efficacy data are still accumulating.

Promising potential: High. The mechanism has opened an active field of research into glutamatergic antidepressants, NMDA receptor modulators, and rapid-acting antidepressant strategies.

Side-effect profile: Dissociation, dizziness, nausea, sedation, hypertension, and perceptual disturbances are common and typically transient (resolving within 2 hours of administration). The compound requires administration in a certified healthcare setting with 2-hour post-dose monitoring due to dissociative and sedative effects. Abuse potential is recognized (ketamine is a Schedule III controlled substance). The safety profile is distinctly less favorable than tianeptine for chronic daily self-administration.

Overall validation: High. FDA-approved for two indications with substantial Phase 3 data. However, the requirement for in-clinic administration, the monitoring requirements, and the cost limit practical accessibility.

Comparison to tianeptine: Tianeptine and esketamine represent two distinct approaches to glutamatergic modulation in depression. Tianeptine modulates AMPA receptor trafficking indirectly through MOR-dependent mechanisms; esketamine directly antagonizes NMDA receptors and secondarily upregulates AMPA signaling. Tianeptine is suitable for chronic daily oral self-administration; esketamine requires intermittent in-clinic intranasal administration. Esketamine offers rapid onset (hours) in treatment-resistant cases; tianeptine requires 2 to 4 weeks for full therapeutic effect. The two compounds are mechanistically complementary rather than competitive.

12.4 Vortioxetine (Trintellix)

Mechanism: Multimodal serotonergic agent. Inhibits the serotonin transporter (SERT) and has direct activity at multiple serotonin receptor subtypes: 5-HT₃ antagonist, 5-HT₇ antagonist, 5-HT_{1D} antagonist, 5-HT_{1B} partial agonist, and 5-HT_{1A} agonist. The multimodal profile is proposed to produce cognitive enhancement beyond the antidepressant effect.

Development trajectory: Developed by Lundbeck and Takeda. Approved by the FDA in 2013 for major depressive disorder. Post-approval studies have emphasized cognitive endpoints, with demonstrated improvements in processing speed, execu-

tive function, and attention in depressed patients.

Novelty: Moderate. The multimodal serotonergic mechanism represents an incremental advance over pure SSRI pharmacology but remains within the serotonergic framework.

Effect size: Moderate. Meta-analyses place vortioxetine effect sizes at approximately 0.2 to 0.4 versus placebo on the MADRS, with dose-response across the 5 to 20 mg range [35]. Cognitive effect sizes (Digit Symbol Substitution Test) are modest but statistically significant, approximately Cohen's d of 0.25 to 0.35.

Promising potential: Moderate to high. The cognitive enhancement claim differentiates vortioxetine from other antidepressants and is of increasing interest in the context of cognitive symptoms of depression.

Side-effect profile: Nausea is the principal adverse event (approximately 20 to 30 percent at 10 to 20 mg doses), dose-dependent and typically transient. Sexual dysfunction rates are lower than SSRIs. Weight effects are neutral. Cardiovascular safety is favorable.

Overall validation: High. FDA-approved with substantial clinical evidence base including cognitive endpoints.

Comparison to tianeptine: Both compounds offer tolerability advantages over classical antidepressants. Vortioxetine has the advantage of FDA approval, cognitive enhancement data, and absence of abuse liability. Tianeptine has the advantage of a distinct (non-serotonergic) mechanism of action, very low sexual dysfunction rates, and potential utility in SSRI-non-responsive patients. Vortioxetine's higher nausea rate at effective doses is a practical tolerability limitation relative to tianeptine.

12.5 Buprenorphine/Samidorphan (ALKS 5461)

Mechanism: Combination of buprenorphine (mu-opioid receptor partial agonist, kappa-opioid receptor antagonist) with samidorphan (mu-opioid receptor antagonist) at a ratio designed to produce kappa-opioid antagonism and blunted mu-opioid agonism. The kappa-opioid antagonist component is hypothesized to mediate the antidepressant effect through modulation of dynorphin/kappa circuits involved in anhedonia and dysphoria.

Development trajectory: Developed by Alkermes as ALKS 5461 for adjunctive treatment of major depressive disorder in patients with inadequate response to standard antidepressants. Phase 3 trials (FORWARD-3, FORWARD-4, FORWARD-5) produced mixed results: FORWARD-5 met its primary endpoint, but FORWARD-3 did not, and FORWARD-4 showed a non-significant trend [36]. The FDA issued a Complete Response Letter in 2019 requesting additional efficacy data. As of 2026, the compound has not received FDA approval for depression.

Novelty: High. The opioidergic mechanism for depression is directly relevant to tianeptine's pharmacology and represents the most mechanistically aligned comparator.

Effect size: Modest and inconsistent across Phase 3 trials. The FORWARD-5 trial demonstrated approximately 2-point MADRS separation from placebo, a statistically significant but clinically modest effect. The inconsistency across Phase 3 trials has raised questions about the reliability of the effect.

Promising potential: Low to moderate. The regulatory path has stalled, and the inconsistent Phase 3 results have dampened enthusiasm. However, the opioidergic mechanism for depression remains an active area of investigation.

Side-effect profile: Nausea, constipation, and dizziness are the most common adverse events. The samidorphan component is designed to block the abuse potential of buprenorphine; the combination has demonstrated no significant abuse liability or physical dependence in clinical trials. This stands in contrast to tianeptine, where the full MOR agonism at supratherapeutic doses creates abuse potential.

Overall validation: Moderate. Extensive Phase 3 clinical program with mixed results. Not FDA-approved.

Comparison to tianeptine: The two compounds share an opioidergic mechanism of antidepressant action but differ critically in MOR pharmacology: tianeptine is a full MOR agonist with dose-dependent abuse liability, while ALKS 5461 uses a partial agonist/antagonist combination designed to minimize abuse potential. The ALKS 5461 approach directly addresses tianeptine's principal safety liability (abuse potential) through a pharmacological strategy (blunted MOR activation via antagonist co-formulation). The inconsistent Phase 3 results for ALKS 5461 may reflect the challenge of producing sufficient MOR-mediated antidepressant efficacy while simultaneously blocking the rewarding properties that drive the MOR engagement.

12.6 Comparator summary

The five compounds occupy distinct positions in the antidepressant pharmacology space. **Imipramine** represents the classical tricyclic reference with high efficacy but limiting tolerability. **Fluoxetine** represents the SSRI standard with proven efficacy, broad approval, and no abuse liability but with sexual dysfunction and activation as limitations. **Esketamine** represents the rapid-acting glutamatergic approach with high novelty and large acute effect sizes but with administration burden and monitoring requirements. **Vortioxetine** represents the multimodal serotonergic approach with cognitive enhancement and favorable tolerability. **Buprenorphine/samidorphan** represents the most mechanistically aligned comparator as an opioidergic antidepressant with engineered abuse mitigation.

Tianeptine occupies a unique position: it is the only approved antidepressant whose primary mechanism is full mu-opioid receptor agonism, the only approved antidepressant with demonstrated effects on AMPA receptor surface trafficking as a secondary mechanism, and the only approved antidepressant with a CYP-independent metabolic pathway that minimizes pharmacokinetic drug interactions. These pharmacological distinctions are counterbalanced by the abuse liability signal that has prevented approval in the United States, Canada, and Australia and that has driven scheduling action in an increasing number of jurisdictions.

The practical positioning of tianeptine is therefore as a well-validated antidepressant with unique pharmacology that is optimally suited for patients who have not responded to serotonergic agents, who experience intolerable sexual dysfunction on SSRIs, who require minimal drug-drug interaction potential, or who have cardiovascular comorbidity that precludes classical tricyclic use. The abuse liability requires clinical monitoring and appropriate patient selection, and the evolving regulatory landscape may further constrain availability.

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