Review Article

The Role of Levosulpiride in the Management of Diabetic Gastroparesis: A Comprehensive Clinical and Pharmacological Review

Kausik Maji[1],Sridhar Panda[2],Subarna Kumar Mallick[3], Aakanksha Jha[4]

1. Professor & Head, Department of Medicine, IIMSAR & Dr Bidhan Chandra Roy Medical College, Haldia, Purba Medinipur, West Bengal
2. Associate Professor, Department of Medicine, SCB Medical College, Cuttack, Odisha
3. Assistant Professor, Department of Medicine, Saheed Rendo Majhi Medical College & Hospital, Bhawanipatna, Odisha
4.Resident, Department of general Surgery, Institute of Medical Sciences and SUM Hospital, Bhubaneshwar

Abstract: Diabetic gastroparesis (DMGP) is a debilitating, chronic manifestation of gastrointestinal autonomic neuropathy that complicates the clinical course of both type 1 and type 2 diabetes mellitus. Characterized by delayed gastric emptying in the absence of mechanical obstruction, its classic presentation includes intractable nausea, vomiting, postprandial fullness, early satiety, and severe abdominal bloating. Beyond its profound negative impact on patient quality of life, DMGP disrupts the synchronization between gastrointestinal nutrient absorption and the pharmacokinetic profiles of exogenous or endogenous insulin, leading to volatile glycemic excursions and unexplained hypoglycemic episodes. Traditional prokinetic agents are clinically bottlenecked by severe extrapyramidal risks (metoclopramide) or cardiotoxicity (cisapride, domperidone). Levosulpiride, a substituted benzamide derivative and the purified levorotatory enantiomer of sulpiride, offers a targeted approach through a distinct dual mechanism: selective peripheral dopamine D2 receptor antagonism and moderate serotonin 5-HT4 receptor agonist activity. This comprehensive review synthesizes the molecular pathophysiology of DMGP, details the pharmacodynamics and pharmacokinetics of levosulpiride, evaluates extensive clinical evidence regarding its symptom-reduction and gastric-emptying capabilities, analyzes its unique advantages in stabilizing long-term glycemic control (HbA1c), and outlines its safety profile, including emerging therapeutic hypotheses like the prolactin/vasoinhibin axis in diabetic retinopathy.

Keywords:- Diabetic gastroparesis ,Gastric emptying delay, Levosulpiride, Dopamine D2 antagonism ,5-HT4 receptor agonist,Glycemic control (HbA1c)

Address for correspondence: Subarna Kumar Mallick, Assistant Professor, Department of Medicine, Saheed Rendo Majhi Medical College & Hospital, Bhawanipatna, Odisha

E-Mail: subarnamallickiyf@gmail.com **Contact: +91-94387-21399**

1.Introduction

Diabetic gastroparesis (DMGP) represents one of the most challenging and poorly managed microvascular/neurodegenerative complications of long-standing diabetes mellitus [(1)]. Broadly classified under the umbrella of diabetic gastroenteropathy, DMGP is defined by objectively delayed gastric emptying of solids and liquids in the absolute absence of a mechanical outlet obstruction or tumor [(2)]. Estimates suggest that up to 40% of type 1 diabetic patients and up to 30% of type 2 diabetic patients experience some degree of altered gastric transit, with a significant cohort developing highly debilitating, chronic upper gastrointestinal symptoms [(3)].

The presentation of DMGP goes far beyond basic indigestion. Patients regularly suffer from severe postprandial fullness, early satiety (the inability to finish a normal-sized meal), recurrent nausea, retching, and intractable vomiting of undigested food consumed hours prior [(4)]. These symptoms fundamentally alter a patient's dietary habits, frequently leading to severe nutritional deficiencies, unintended weight loss, and recurrent hospitalizations due to dehydration and acute electrolyte imbalances [(5)].

Crucially, the delayed and highly unpredictable evacuation of chyme from the stomach into the duodenum creates a severe metabolic mismatch. Because the delivery of carbohydrates to the absorptive mucosal surfaces of the small intestine is decoupled from the predictable onset of action of subcutaneous insulin or oral hypoglycemic agents, patients slide into an unstable cycle of early postprandial hypoglycemia followed by delayed, severe hyperglycemia [(6)].

First-line clinical management has historically relied on prokinetic pharmacotherapy to force gastric motility. However, conventional options are deeply flawed. Metoclopramide, a non-selective D2 antagonist, is severely restricted by regulatory bodies like the U.S. FDA via a "black box" warning due to its high propensity to cross the blood-brain barrier and cause irreversible tardive dyskinesia [(7)]. Domperidone carries prominent warnings regarding QT-interval prolongation and sudden cardiac death

[8]. Older 5-HT4 receptor agonists like cisapride were completely withdrawn from major global markets due to fatal ventricular arrhythmias (torsades de pointes) [9]. Within this therapeutic void, levosulpiride has emerged as a structurally distinct, effective, and safer option for managing both the underlying dysmotility and the sensory symptoms of DMGP [10].

2. Pathophysiology of Diabetic Gastroparesis

The structural and functional degradation of the stomach in diabetes is a complex, multifactorial cascade heavily driven by chronic, uncontrolled hyperglycemia, oxidative stress, and microvascular ischemia.

2.1 Autonomic Neuropathy and Enteric Degeneration

The primary structural defect in DMGP is the selective loss or structural blunting of the unmyelinated vagal fibers that provide parasympathetic, excitatory input to the stomach [1]. Chronic metabolic stress triggers advanced glycation end-products (AGEs) accumulation, leading to microangiopathy of the vaza nervorum. The resulting ischemic injury impairs the vagal nerve's ability to coordinate antral-duodenal contractions and initiate normal fundic accommodation [5]. Without coordinated vagal input, the proximal stomach fails to relax appropriately upon food ingestion (causing early satiety), and the distal antrum suffers from severe hypomotility (antral pump failure).

2.2 Loss of the Interstitial Cells of Cajal (ICC)

The Interstitial Cells of Cajal (ICC) act as the bio-electrical pacemakers of the gastrointestinal tract, generating the intrinsic electrical slow waves (approximately 3 cycles per minute in the human stomach) that dictate the maximum frequency and direction of gastric contractions [11]. Histopathological biopsies from diabetic patients consistently reveal severe depletion, fragmentation, and structural breakdown of the ICC networks within the muscularis propria [12]. The loss of ICCs uncouples electrical propagation, resulting in severe gastric slow-wave dysrhythmias, including tachygastria, bradygastria, and complete electromechanical uncoupling.

2.3 Depletion of Nitrergic Neurons

Normal pyloric relaxation is mediated by non-adrenergic, non-cholinergic (NANC) enteric neurons that release nitric oxide (NO) [11]. Under diabetic stress, there is a selective down-regulation of neuronal nitric oxide synthase (nNOS). The loss of nitrergic inhibitory signaling results in sustained, paradoxical contractions of the pylorus, a phenomenon clinically termed *pylorospasm* [13]. Pylorospasm acts as a physical functional barrier, directly impeding the evacuation of solid food particles into the duodenum.

2.4 Dopaminergic Hyperactivity

Dopamine acts as a potent endogenous inhibitor of upper gastrointestinal tract motility [14]. It binds to inhibitory pre-synaptic and post-synaptic receptors throughout the enteric nervous system, effectively blocking the voltage-gated release of acetylcholine from excitatory motor neurons [10]. In the diabetic state, local dopaminergic tone or eceptor expression is often abnormally upregulated, leading to continuous, inappropriate suppression of antral smooth muscle contractility.

3. Pharmacological Profile of Levosulpiride

Levosulpiride is the chemically pure levorotatory of racemic sulpiride, a substituted benzamide derivative [15]. While racemic sulpiride possesses central neuroleptic properties, the isolated levorotatory isomer exhibits significantly enhanced peripheral tissue selectivity, higher bio-affinity for gastrointestinal receptors, and an entirely different clinical application at low doses [10].

3.1 Dual Mechanism of Action

Unlike conventional mono-targeted prokinetics, levosulpiride achieves its therapeutic effects through a distinct dual-action pharmacological pathway:

Dual Action = Selective Peripheral D2 Receptor Antagonism+ Moderate 5-HT4 Receptor Agonism

1. Selective D2 Receptor Antagonism

At low clinical doses 25 mg three times daily), levosulpiride acts as a highly selective antagonist of dopamine D2 receptors, with preferential affinity for pre-synaptic autoreceptors [14]. By blocking these pre-synaptic D2 receptors on cholinergic nerve endings, levosulpiride removes the endogenous "dopaminergic brake." This uninhibited state significantly accelerates the synthesis and subsequent release of acetylcholine into the neuromuscular junctions of the gastric smooth muscle [15]. The elevated local concentrations of acetylcholine bind to muscarinic M3 receptors, driving coordinated, high-amplitude contractions of the gastric antrum, enhancing lower esophageal sphincter (LES) basal tone, and improving antroduodenal coordination.

Furthermore, levosulpiride acts on post-synaptic D2 receptors located within the area postrema outside the blood-brain barrier—the chemoreceptor trigger zone (CTZ) [10]. This direct central/peripheral anti-dopaminergic action effectively blocks circulating emetogenic triggers, providing rapid, independent relief from nausea and vomiting.

2. Serotonin 5-HT4 Receptor Agonism

Concurrently, levosulpiride acts as a moderate agonist at the serotonin 5-HT4 receptors located on intrinsic primary afferent neurons (IPANs) within the myenteric plexus [9]. Activation of 5-HT4 receptors triggers intracellular adenylyl cyclase activation, elevating cyclic adenosine monophosphate (cAMP) levels, which further amplifies the quantal release of acetylcholine [8]. This secondary pathway works synergistically with D2 blockade to improve fundic accommodation and loosen pylorospasm, facilitating a smooth exit pathway for gastric contents.

3.2 Pharmacokinetics

Following oral administration of a standard 25 mg tablet, levosulpiride exhibits a rapid absorption profile, reaching peak plasma concentration (Cmax) within 1.5 to 2 hours [15]. Its absolute oral bioavailability sits at approximately 30% due to highly specialized, non-saturable intestinal transporter mechanics, and it demonstrates very low plasma protein binding (<10%) [10]. The drug distributes widely into gastrointestinal tissues but exhibits poor lipid solubility, which limits extensive crossing of the healthy blood-brain barrier at low prokinetic doses. Levosulpiride does not undergo significant hepatic metabolism via the cytochrome P450 enzyme matrix; it is excreted primarily unchanged through the

kidneys via glomerular filtration, featuring an elimination half-life (t1/2) of roughly 6 to 8 hours [15]

4. Clinical Efficacy in Symptom Management and Gastric Motility

The clinical deployment of levosulpiride in DMGP is backed by numerous robust, randomized, controlled clinical trials evaluating both subjective symptom indexes and objective, quantitative physiological transit times.

4.1 Resolution of Upper Gastrointestinal Symptoms

The primary goal of therapy from a patient perspective is symptom control. In long-term clinical trials using structured questionnaires like the Gastroparesis Symptom Cardinal Index (GCSI), levosulpiride therapy 25 mg t.i.d. administered 30 minutes before major meals consistently outperformed placebo and traditional prokinetics [16]. In a hallmark trial conducted by Mansi et al. (1995), patients with confirmed diabetic gastroparesis secondary to type 1 or type 2 diabetes were treated with levosulpiride for 16 weeks. The investigators noted a major, statistically significant drop in the cumulative severity scores of early satiety, postprandial bloating, and epigastric pain. The antiemetic efficacy was particularly pronounced, with over 80% of patients reporting a near-complete cessation of daily retching and vomiting episodes within the first 14 days of therapy—an effect directly attributed to the dual benefit of accelerated emptying and CTZ ,D2 receptor blockade [17]. In head-to-head comparative trials against other agents like cinitapride and itopride, levosulpiride demonstrated superior clinical outcomes in eradicating refractory postprandial fullness and bloating [10, 18].

4.2 Objective Acceleration of Gastric Transit Times

To prove that symptomatic relief is tied to a physical resolution of stasis, researchers utilize quantitative imaging. Gastric Emptying Scintigraphy (GES) utilizing a standard, low-fat solid meal labeled with Technetium-99m (^{m}Tc) sulfur colloid represents the diagnostic gold standard.

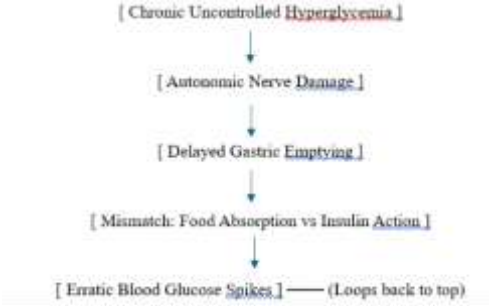
Clinical evaluations confirm that chronic administration of levosulpiride significantly shifts the emptying curve toward normal parameters. In controlled parameters, levosulpiride reduced the mean 50%gastric emptying time (T1/2) of solids from an abnormal pre-treatment baseline of 321 pm 24 minutes down to a highly improved 261 pm 18 minutes ($p < 0.01$) [19]. Real-time 3D ultrasonography of the gastric antrum further confirmed that levosulpiride directly increases both the frequency and the net amplitude of postprandial antral contractions, while simultaneously preventing retrograde duodenogastric reflux [20]. More recently, clinical trials utilizing advanced Lactulose Hydrogen Breath Testing confirmed a significant reduction in total orocecal transit times in severe diabetic cohorts following a standard course of levosulpiride [21].

5. Synchronization of Gastric Emptying and Glycemic Control

Beyond structural comfort, the most profound clinical benefit of levosulpiride in diabetic care is its secondary impact on metabolic stabilization and the reduction of glycemic variability.

5.1 The Vicious Cycle of Dysmotility and Glycemia

The relationship between blood glucose and gastric motility is a bidirectional, pathological feedback loop [22]. Acute hyperglycemia itself acts as an immediate inhibitor of gastric motility; blood glucose concentrations exceeding 180mg/dL 10 mmol/L induce antral hypomotility, prompt pylorospasm, and trigger gastric dysrhythmias even in non-diabetic individuals [6]. Conversely, the resulting delayed, highly erratic delivery of carbohydrates to the duodenum creates a clinical scenario where pre-meal short-acting insulin injections reach peak plasma activity long before the food is broken down and emptied from the stomach, causing unexpected, severe postprandial hypoglycemia [23]. When the stomach finally evacuates its contents hours later, the insulin effect has waned, resulting in severe, prolonged delayed hyperglycemia.



5.2 HbA1c Stabilization via Levosulpiride

By repairing the physical motility defect, levosulpiride breaks this feedback loop. By enforcing predictable, steady postprandial emptying, the appearance of glucose in the portal circulation is successfully synchronised with the pharmacodynamics of insulin or oral therapies [24].

In a landmark, long-term 6-month double-blind clinical trial evaluating insulin-dependent diabetes mellitus (IDDM) patients with severe gastroparesis, Melga et al. (1997) documented that a continuous regimen of levosulpiride (25 mg t.i.d.) induced a profound, sustainable reduction in mean daily plasma glucose levels. Strikingly, the stabilized gastric emptying translated into a statistically significant reduction in glycated haemoglobin (HbA1c) values, dropping from a baseline of 6.7% pm 0.4% down to 5.7% pm 0.3% ($p < 0.05$) without an increase in hypoglycaemic events [19]. This predictable kinetic alignment allows endocrinologists to safely down-titrate or optimize insulin dosing regimens, dramatically reducing overall glycemic variability.

6. Safety, Tolerability, and Neuro-Hormonal Interactions

While levosulpiride exhibits an excellent clinical track record, its distinct anti-dopaminergic mechanism dictates a specific, highly predictable profile of side effects that requires diligent clinical understanding.

6.1 Extrapyramidal Symptom (EPS) Risk Profile

Because levosulpiride blocks dopamine D2 receptors, it carries a potential risk of inducing extrapyramidal symptoms (EPS) if the drug crosses the blood-brain barrier in high concentrations or if used in highly susceptible patient populations [25]. Clinical presentations can include drug-induced

Parkinsonism (tremor, rigidity, bradykinesia), akathisia, acute dystonia, and very rarely, tardive dyskinesia [26].

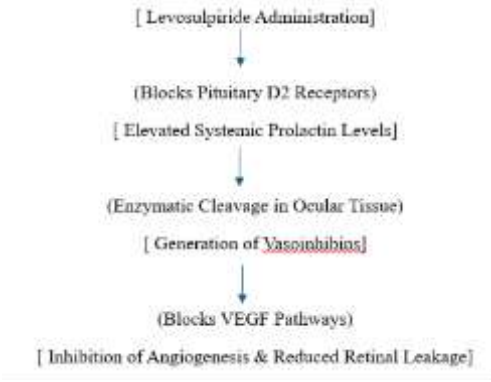
However, prospective epidemiological assessments reveal that at the low, targeted dose of 75 mg/day utilised for gastroenterological indications, the incidence of severe EPS is exceptionally low, particularly when compared to metoclopramide [7]. Metoclopramide features high lipid solubility and unselective central penetrance, whereas levosulpiride's highly polar molecular structure restricts substantial central accumulation [10]. Nonetheless, caution must be exercised, and regular neurological monitoring is warranted when prescribing levosulpiride to elderly diabetic patients, who possess inherently vulnerable blood-brain barriers and decreased renal clearance pathways [26].

6.2 Hyperprolactinemia and the Prolactin/Vasoinhibin Axis

The most frequent endocrine side effect observed with levosulpiride therapy is hyperprolactinemia [16]. Dopamine acts centrally as the primary prolactin-inhibiting factor via lactotroph receptors in the anterior pituitary gland, which sits outside the endothelial blood-brain barrier. Levosulpiride-mediated blockade leads to an uninhibited, rapid rise in systemic prolactin levels [15]. Clinically, this can manifest as galactorrhea, breast engorgement, gynecomastia, and reversible menstrual irregularities [16]. While these symptoms often resolve promptly upon drug down-titration or temporary cessation, this hyperprolactinemic pathway has sparked groundbreaking medical interest regarding microvascular protection.

The Prolactin/Vasoinhibin Hypothesis in Diabetic Retinopathy

Diabetic retinopathy (DR) and diabetic macular edema (DME) represent primary causes of irreversible blindness, driven by ischemia-induced upregulated vascular endothelial growth factor (VEGF), which leads to pathological intraocular angiogenesis and blood-retinal barrier breakdown [27]. Extensive research has established that systemic prolactin is enzymatically cleaved within ocular tissues by matrix metalloproteinases and cathepsin D into smaller, highly potent anti-angiogenic fragments called *vasoinhibins* [27].



Vasoinhibins directly bind to endothelial cell receptors, blocking VEGF-induced nitric oxide production, halting endothelial cell proliferation, and closing leaky capillary tight junctions [27]. Consequently, the controlled elevation of systemic prolactin via low-dose levosulpiride is currently being leveraged in clinical designs as a novel, protective therapeutic strategy to suppress angiogenesis and reduce macular edema in patients suffering from advanced diabetic retinopathy [27]. This presents a unique clinical paradigm where a drug's endocrine side effect directly serves to mitigate a separate microvascular complication of the same disease state.

8. Clinical Recommendations and Future Directions

For maximum therapeutic benefit, levosulpiride should be initiated at a conservative oral dose of 25 mg three times daily, ingested strictly 30 minutes prior to breakfast, lunch, and dinner. This timing ensures that peak plasma concentrations (max) perfectly coincide with the entry of food into the stomach, maximizing coordinated antral contractions. If a patient presents with a severe acute exacerbation of gastroparesis where oral intake is completely compromised by unceasing vomiting, the therapy can be initiated via intravenous or intramuscular routes(25 mg b.i.d.) for 3 to 5 days until stabilization permits a transition back to oral tablets.Given its long-term excretion profile, dosage adjustments are mandatory in patients demonstrating stage 3 or greater chronic kidney disease (GFR< 60mL/min/1.73m^2) to avoid systemic accumulation and reduce the risk of extrapyramidal complications. Future large-scale, multi-center, double-blind trials are currently focused on evaluating the combined long-term benefits of levosulpiride on both gastric physiological motility and the quantitative stabilization of diabetic retinopathy markers over a multi-year period.

9. Conclusion

Diabetic gastroparesis stands as a complex, multi-layered complication requiring a therapy that targets both mechanical delay and central sensory symptoms. Levosulpiride successfully achieves this standard through its synergistic dual mechanism of selective dopamine D2 receptor antagonism and serotonin 5-HT4 receptor agonism. Extensive clinical evidence supports its ability to significantly alleviate upper gastrointestinal symptom burdens, decrease objective solid food gastric retention times, and dramatically improve overall postprandial glycaemic control—as evidenced by significant reductions in long-term HbA1c levels. Combined with a safer neurological profile than metoclopramide and lacking the prominent cardiotoxic threats of domperidone, levosulpiride represents a highly effective, evidence-based choice in the modern therapeutic management of diabetic gastroparesis.

7. Comparative Assessment: Levosulpiride vs. Conventional Prokinetics

To provide clear clinical guidance, it is essential to compare levosulpiride against alternative prokinetic choices currently available in modern clinical practice:

Drug Name	Primary Pharmacodynamic Mechanism	Clinical Superiority in DMGP	Major Clinical Bottlenecks & Side Effects	Regulatory Status & Safety Warnings
Levosulpiride	Selective D_2 Antagonism + Moderate 5-HT_4 Agonism	High antiemetic and antral motility potency; improves HbA1c curves; possible retinal benefits	Hyperprolactinemia (galactorrhoea, gynecomastia); low EPS risk	Widely approved; caution in elderly and renal patients
Metoclopramide	Non-selective D_2 Antagonism + 5-HT_4 Agonism	Widely available; potent immediate antiemetic	High CNS penetration; tardive dyskinesia, depression, anxiety	FDA Black Box Warning; restrict use to ≤12 weeks
Domperidone	Peripheral D_2 Receptor Antagonism	Minimal BBB crossing; very low EPS risk	Risk of cardiac ventricular arrhythmias and sudden cardiac death	EMA restrictions; limited dose and duration
Itopride	D_2 Antagonism + Acetylcholinesterase (AChE) Inhibition	Minimal CNS penetration; no QT prolongation	Lower efficacy in severe gastroparesis-induced vomiting	Well tolerated; mainly used in mild–moderate dyspepsia
Cinitapride	5-HT_4 Agonist + Moderate D_2 Antagonism	Good neurological safety profile	Tachyphylaxis (reduced effect over time)	Approved in select European & Asian markets; secondary option

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Abbreviations

DG – Diabetic Gastroparesis
ICC – Interstitial Cells of Cajal
CNS – Central Nervous System
5-HT4 – 5-Hydroxytryptamine 4
D2 – Dopamine D2 Receptor
GI – Gastrointestinal

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