

Review

Metoclopramide in Gastroparesis: Its Mechanism of Action and Safety Profile

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Abstract: Metoclopramide has been the cornerstone of gastroparesis management for the past 40 years as it is the only FDA-approved medication for gastroparesis. Other medications such as erythromycin and domperidone have been used off-label with variable efficacy. Historically, metoclopramide has been used in oral, intravenous, and subcutaneous formulations. It is an antiemetic and prokinetic medication that acts through the inhibition of central (chemoreceptor trigger zone) and peripheral dopaminergic and serotogenic receptors. Due to its antidopaminergic effects, extrapyramidal symptoms have been reported, with the most feared adverse event being tardive dyskinesia. Subsequently, the FDA issued a metoclopramide black box warning label in February 2009 due to its risk of causing tardive dyskinesia, which can be irreversible. The incidence and prevalence of tardive dyskinesia among metoclopramide users have been variable in different studies. However, upon review of the current literature, the true prevalence of tardive dyskinesia seems to be lower than previously thought. This review will focus on metoclopramide and the extrapyramidal symptoms associated with its use.



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1. Introduction

The discovery of metoclopramide was a fortunate stroke of serendipity. It was synthesized during a trial that aimed to better understand the properties of procainamide, an antiarrhythmic drug. A simple substitution of a benzene ring gave rise to its antiemetic properties without the local anesthetic or cardiac antiarrhythmic activity of procainamide [1].

The medication has been a staple in US markets since 1979 and is now available in oral, subcutaneous, intravenous, and, most recently, intranasal forms [2].

It is the undefeated champion in the treatment of gastroparesis (GP) as it is the only FDA-approved medication for GP treatment in the past 40 years. Its widespread use has even earned it a place on the World Health Organization's List of Essential Medicines—the most effective and safe medicines needed in a health system [3].

2. Mechanism of Action

Metoclopramide exerts both central and peripheral actions in the treatment of GP. One mechanism of action is at the chemoreceptor trigger zone (CTZ) to suppress the vomiting reflex by inhibiting 5HT₃ and D₂ receptors. Peripherally, it antagonizes presynaptic D₂ and muscarinic receptors, inhibits postsynaptic D₂ receptors, and stimulates presynaptic 5HT₄ receptors, resulting in increased acetylcholine release [1].

2.1. Summary of D2 Antagonism

1. CTZ—D2 receptors are found in the CTZ in the area postrema of the fourth ventricle. The area lies outside the blood–brain barrier and is therefore susceptible to drugs or toxins that can initiate vomiting. Metoclopramide is able to achieve its antiemetic effect specifically by inhibiting the vomiting pathway (CTZ). Irritant stimuli from the GI tract travel via visceral afferent nerves to the central nervous vagal motor neurons causing salivation, gastric relaxation, retrograde small bowel contractions, diaphragmatic contraction, and opening of the esophageal hiatus. By exhibiting D2 antagonism, metoclopramide is able to prevent the aforementioned cascade of events.
2. Striatal Effects—D2 receptors are found in the indirect striatopallidal projection, which are pathways that regulate the basal ganglia output to control movement. Therefore, extrapyramidal side effects including tardive dyskinesia can occur with metoclopramide.
3. Pineal Gland—Metoclopramide also blocks D2 receptors in the pineal gland, resulting in increased release of prolactin which can result in hypogonadism.
4. GI tract—Dopaminergic effects on the GI tract include decreased lower esophageal sphincter (LES) pressure, decreased antral muscle contractility, decreased coordination of gastroduodenal motility, and delayed gastric emptying. This effect is inhibited by the pre and postsynaptic antidopaminergic action of metoclopramide. It should be remembered that metoclopramide was first approved for gastroesophageal reflux disease (GERD) based on its ability to increase LES pressure which helps reduce reflux symptoms.

2.2. Summary of 5HT4 Agonist Activity

Metoclopramide's 5HT4 receptor agonist properties work peripherally in the gastric smooth muscle to increase the release of acetylcholine from enteric cholinergic neurons. This prokinetic property results in increased duodenal peristalsis, increased gastric emptying, and decreased esophageal reflux [4].

2.3. Summary of 5HT3 Antagonism

Metoclopramide blocks the 5HT released from mucosal enterochromaffin cells in the upper GI tract and therefore prevents the activation of 5HT3 receptors in the abdominal vagal nerve terminals. This results in the inhibition of the emetic stimulatory actions of 5HT and other cytotoxic substances on the vagal nerves.

Selective 5HT3 receptor antagonists have been effective as antiemetics and are used in treating chemotherapy-induced nausea and vomiting.

3. Pharmacokinetics

When taken orally, metoclopramide is approximately 85% absorbed in the GI tract. It undergoes variable first-pass metabolism with a bioavailability ranging between 60 and 90% and reaches peak plasma concentration (T_{max}) within 1–4 h when administered as a modified-release tablet. Once absorbed, it is distributed primarily in the liver, biliary tract, intestinal mucosa, salivary glands, and area postrema. A total of 40% of the medication is protein bound and has linear plasma pharmacokinetics at oral doses from 5 to 20 mg [5].

The large variation in oral bioavailability can be attributed to its metabolism to monodeethylmetoclopramide by the cytochrome P450 system, largely by the CYP2D6 isoform. Genetic polymorphisms of the enzymes have been linked to a predisposition to tardive dyskinesia [6]. Interestingly, metoclopramide is also a competitive inhibitor of this specific isoform. Other neuroleptic agents like perphenazine, haloperidol, and chlorpromazine also competitively inhibit this isoform. Therefore, the concomitant administration of those medications with metoclopramide may lead to increased plasma concentrations, predisposing a patient to the development of tardive dyskinesia. Patients with GP often have other coexisting conditions such as diabetes and psychiatric illnesses which puts them at an increased risk of polypharmacy. A large number of medications (approximately 30%) are substrates of CYP2D6, such as opioids, antidepressants, and various cardiac medications, putting

patients who are taking metoclopramide at an increased risk of drug–drug interactions [2]. The clearance of metoclopramide is also affected by cirrhosis and renal failure. About 24% of the drug is excreted in urine without undergoing first-pass metabolism, leading to a longer half-life and decreased clearance by 50% in patients with renal failure [7].

4. Metoclopramide Uses

Nearly 40 years ago, the FDA approved metoclopramide use for the treatment of symptomatic, documented gastroesophageal reflux for 4–12 weeks in adults who fail to respond to conventional therapy and for the relief of symptoms in adults with GP. Metoclopramide, however, has many off-label uses which will be discussed below.

Metoclopramide has been used as a prophylactic agent for chemotherapy-related nausea and vomiting. A randomized double-blinded clinical trial was conducted to highlight its efficacy as an antiemetic versus the efficacy of dexamethasone and lorazepam. The study showed that while the combination of dexamethasone and lorazepam can control emesis in 25% of patients receiving variable emetogenic chemotherapy such as cisplatin, the addition of metoclopramide provided relief in up to 67% of patients. Its use also resulted in extrapyramidal reactions in 11.5% of patients and is therefore not a first-line agent [8].

Large trials have also shown that metoclopramide has efficacy in hyperemesis gravidarum. In a randomized double-blind trial conducted including 160 women with hyperemesis gravidarum, 80 women were randomized to be treated with 4 mg IV ondansetron, with the other half treated with 10 mg metoclopramide every 8 h for 24 h. The women were asked to keep an emesis diary and the results showed that ondansetron and metoclopramide demonstrated similar antiemetic effects. The drawbacks of metoclopramide use in the study were the side effects, which did not include any movement-related adverse effects, which can be attributed to the study duration (24 h period) [9].

Moreover, a randomized controlled trial comparing the efficacy of promethazine with metoclopramide for hyperemesis gravidarum in 149 women showed a favorable adverse effect profile in patients receiving metoclopramide [10].

Metoclopramide has also been given experimentally for migraines due to its D2 receptor antagonism effect. It is used to treat symptoms of nausea and vomiting seen in acute migraines, which are thought to be associated with gastric stasis, which can impair the absorption of medications administered for migraines [11,12]. These effects make metoclopramide an ideal medication for short-term therapy in acute migraine management. The American Headache Society deemed 10 mg metoclopramide to be highly effective compared to opioids for the management of acute migraine in the emergency department [13].

Multiple case reports have shown benefits in using metoclopramide therapy in refractory Diamond Blackfan Anemia in combination with the standard corticosteroid therapy and blood transfusions. The lifelong recurrent blood transfusions required in these patients lead to multiple complications such as iron overload. Metoclopramide reduces this risk by increasing the release of prolactin from the pituitary which stimulates erythropoiesis and, hence, decreases the requirement for blood transfusions [14].

5. Formulations of Metoclopramide

Metoclopramide is typically administered orally as a tablet or in liquid form, prior to meals and/or sleep. It can also be given intramuscularly, intravenously, or rectally in patients with severe nausea or vomiting. In addition, an intraperitoneal formulation of metoclopramide can be used in patients undergoing peritoneal dialysis [15].

Intranasal formulations of metoclopramide have been developed as an antiemetic and prokinetic with similar pharmacokinetics when compared to intravenous and intramuscular formulations. Multiple trials have shown that side effects include minor irritation of the nasal membrane and dysgeusia. However, no extrapyramidal side effects associated with metoclopramide were reported by any of the 89 subjects in the study [16]. It is important to note that this formulation has been recently FDA approved and long-term data are limited. The use of intranasal metoclopramide can be of particular importance in GP patients due

to the concern of decreased and unpredictable absorption of metoclopramide in patients with decreased gastric emptying who also may be vomiting [17].

6. Metoclopramide Adverse Events

Adverse events are a cause of concern and have led to a decrease in the utilization rates of this medication. A medical record review was conducted in 2013 to evaluate the rates of reported metoclopramide-related tardive dyskinesia and utilization before and after the issuance of the black box warning by the FDA. Following the black box warning, the rates of metoclopramide use for GP dropped from 69.8% to 23.7% with an increase in the number of domperidone prescriptions. Moreover, most of the adverse event reporting of tardive dyskinesia was lawyer initiated, indicating a possible bias in adverse event reporting [18].

Metoclopramide side effects primarily arise from its ability to cross the blood–brain barrier and, hence, can result in a range of clinical symptoms ranging from depression to movement-related disorders (Figure 1).

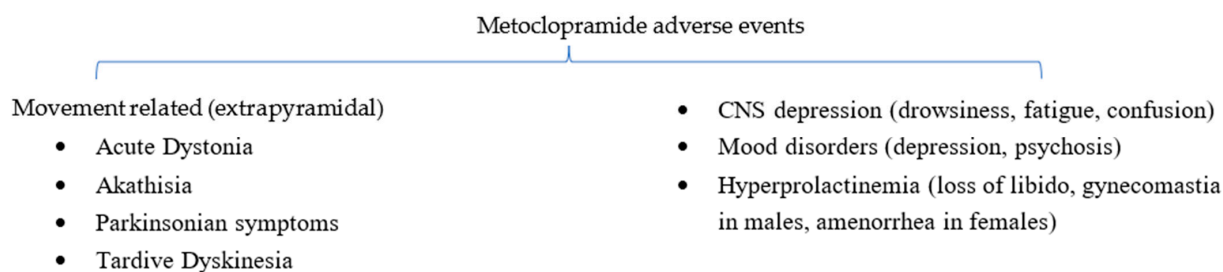


Figure 1. Metoclopramide adverse events classification.

An animal-based study was conducted in 2006 evaluating the penetrance of the blood–brain barrier by different anti-emetics that showed that metoclopramide had 100% penetrance [19]. The side effects of metoclopramide can be divided broadly into two categories: extrapyramidal side effects and non-extrapyramidal side effects. In this review, movement-related disorders or extrapyramidal side effects will be the primary focus as they are the likely reasons for metoclopramide avoidance or discontinuation.

Extrapyramidal side effects include; acute dystonia, akathisia, Parkinsonian symptoms, and the most feared complication, tardive dyskinesia. Certain patient populations are found to be at increased risk, such as age > 60, pediatric patients (dystonia specifically), females, concomitant use of neuroleptic medications, prolonged treatment duration (>12 weeks), history of diabetes mellitus, renal insufficiency, use of CYP2D6 inhibitors, and genetic predisposition due to decreased CYP2D6 metabolism (Table 1) [6].

Table 1. Predisposing factors for metoclopramide extrapyramidal side effects.

Predisposing Factors for Extrapyramidal Side Effects
Elderly population (age > 60)
Pediatric population–acute dystonia
Female sex
Use of neuroleptic medications (e.g., 1st generation antipsychotics)
Treatment duration > 12 weeks
Total dose > 30 mg daily
Diabetes mellitus
Renal or hepatic dysfunction
Use of CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, and bupropion)
Genetic (decreased CYP2D6 metabolism)

6.1. Acute Dystonic Reactions

Dystonic reactions are the result of involuntary sustained muscle contraction and have variable presentations, such as oculogyric crisis, torticollis, and retrocollis. Symptoms can be segmental, focal, or generalized. Drug-induced dystonia is generally focal, with involvement of the head region primarily. Drug-induced dystonic reactions are one of the most common adverse events of metoclopramide use. However, prevalence has not been accurately estimated for dystonic reactions, likely due to their transient and self-resolving nature. It is estimated that up to 6% of patients experience acute dystonia. Acute dystonia generally occurs within 24–72 h of medication administration [20]. The proposed mechanism is thought to be due to an imbalance between dopaminergic and cholinergic stimulation secondary to the D2 blockade, leading to disordered muscle contraction.

Symptoms generally resolve with metoclopramide discontinuation and in cases of significant discomfort, centrally acting anticholinergics such as benztropine and trihexyphenidyl or antihistamines with anticholinergic activity such as diphenhydramine can help alleviate symptoms. Intravenous and intramuscular administration is preferable secondary to significant first-pass metabolism through the oral route [21]. Benzodiazepines have shown some efficacy in smaller studies, with approximately 23% of patients showing improvement with clonazepam. Hence, their use can be considered after risk–benefit analysis on a case-by-case basis [22].

Botulinum toxin injection is another option for the management of dystonias, however, is generally not required due to its transient nature. It acts through inhibition of acetylcholine release at the neuromuscular junction which is increased in cases of drug-induced dystonia secondary to D2 receptor blockade and cholinergic excitation [23].

6.2. Akathisia

Akathisia is a neuropsychiatric disorder presenting with an increased restlessness sensation (generally in the lower extremities), psychomotor agitation, and anxiety. It is largely medication-induced with the primary culprit drug class being antipsychotics, specifically first-generation antipsychotics. Metoclopramide is another cause of akathisia due to dopaminergic inhibition [24]. In addition, benzodiazepine withdrawal is another cause of akathisia. Studies evaluating akathisias are scarce, possibly due to the difficulty in diagnosis, and possible progression to other movement-related disorders. A prospective study in 1994 by Sachdev et al. evaluated the incidence of drug-induced akathisia in patients receiving antipsychotics over a two-week period. Approximately 60% of patients developed akathisia, with the majority suffering from mild symptoms [25]. Akathisia generally occurs within days to weeks of drug initiation. The exact pathophysiology of akathisia remains unclear; even though a dopaminergic and cholinergic imbalance exists, akathisia does not improve with the use of anticholinergics. A proposed mechanism is that after continued use, the hypersensitization of D2 receptors in the nigrostriatal pathway occurs which results in restlessness. Theoretically, this implies that an increase in the dosage of the medication could relieve akathisia; however, this increases the risk of tardive dyskinesia and, hence, is never practiced. This phenomenon can also lead to psychosis following medication discontinuation [26]. Akathisia management involves a dosage decrease in the culprit medication in addition to a beta-blockade, generally with propranolol. Due to the efficacy of propranolol in the treatment of akathisia, theories have emerged regarding central dopaminergic and beta-adrenergic imbalances [27]. Benzodiazepines were also studied and compared to beta blockers; however, they were found to be inferior to beta blockers in akathisia management [28]. A randomized double-blinded clinical trial by Regan A. in 2009 evaluated the incidence of akathisia in patients receiving bolus infusions over 2 min versus slower infusions over 15 min. Akathisia developed in 11.1% of patients in the bolus group versus 0% in patients in the slow rate group [29].

6.3. Parkinsonian Symptoms

Drug-induced parkinsonism is a known complication in patients on dopaminergic receptor blockers. It is characterized by bradykinesia, rigidity, and a resting tremor. Parkinsonian symptoms occur as a result of a D2 blockade in the nigrostriatal pathway similar to that in idiopathic parkinsonism. Patients receiving dopamine-blocking medications had a four-fold higher risk of developing Parkinsonian symptoms [30]. A case-control study with approximately 20,000 participants was performed to evaluate the association between metoclopramide use and antiparkinsons therapy prescriptions. The study concluded that patients on metoclopramide were 3× more likely to be prescribed antiparkinson medication when compared to the control group. In addition, the use of anticholinergic medications was also higher in metoclopramide users, likely owing to the development of extrapyramidal symptoms [31]. This study shows that clinical suspicion and accurate history can prevent this reversible side effect and decrease patient burden and the risk of side effects from polypharmacy. Treatment of drug-induced parkinsonism is through medication discontinuation; anticholinergics can help in the interim as symptoms take 2–3 months to resolve.

6.4. Tardive Dyskinesia

Tardive dyskinesia will be discussed in greater detail as it is irreversible and causes significant patient burden and morbidity, in addition to being a common cause of lawsuits. Metoclopramide-associated tardive dyskinesia accounts for one-third of drug-induced movement disorders. Metoclopramide is the only FDA-approved medication for GP due to its prokinetic activity and efficacy in clinical trials. As such, the use of metoclopramide increased significantly in the 1980s and decreased in the 1990s due to the approval of cisapride for GERD and off-label use in gastroparesis, in addition to the increased recognition of metoclopramide-associated movement-related disorders. In the year 2000, cisapride was withdrawn from the US market due to an increased incidence of cardiac arrhythmias, which led to a surge in metoclopramide use [32].

In February 2009, the FDA issued a black box warning label stating “Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose. Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.”

The true incidence and prevalence of metoclopramide-induced tardive dyskinesia have been variable in different studies.

A Swedish national database review by Wiholm et al. over a five-year period included 11 million prescriptions. The study revealed that the incidence of tardive dyskinesia amongst metoclopramide users was 1 in 2000–2800 patient-years, with an average duration of use of 14 months [33]. A retrospective review of the UK national database by Bateman et al. assessed the prevalence of metoclopramide-induced tardive dyskinesia. The risk of tardive dyskinesia was <0.1%, with 478 cases of metoclopramide-associated extrapyramidal symptoms out of a total of 15.9 million prescriptions. Of those, only four cases of tardive dyskinesia were diagnosed, with an estimated tardive dyskinesia risk of 1 in 2000 patient-years. However, this percentage should be assessed with caution as the study did not differentiate patients with respect to the duration of metoclopramide use [20]. A retrospective review by Ganzini et al. at the Veterans Affairs evaluated the risk of metoclopramide-induced tardive dyskinesia. The study found that 29.4% of metoclopramide users developed tardive dyskinesia. However, the sample size was too small

(51 participants) in this study to draw any conclusions. Moreover, even though the relative risk was elevated at 1.67, there was no statistical significance noted [30].

A cross-sectional study in the Veterans Affairs (VA) by Sewell et al. evaluated 51 patients on metoclopramide and matched them to 31 non-metoclopramide users. A total of 27% of patients on metoclopramide developed tardive dyskinesia versus 12% in non-users (p -value 0.08). It is important to note that the sample size was small, and there was no statistical significance noted. However, diabetic patients on metoclopramide were more likely to develop tardive dyskinesia (p -value 0.05) [34].

A single-center retrospective review by Kenney et al. in 2008 evaluated the prevalence of tardive dyskinesia between the years 1981 and 2006. In the aforementioned period, 23,653 movement-related disorders were diagnosed, of which 434 cases of tardive dyskinesia were diagnosed. Approximately 40% of patients with tardive dyskinesia had a history of metoclopramide use. However, this study did not evaluate the risk of tardive dyskinesia due to metoclopramide as it only evaluated patients with tardive dyskinesia and, hence, the risk might be exaggerated as no control group (metoclopramide users without movement-related disorders) was included [35].

A retrospective review of medical claims data between 2001 and 2010 by Merrill et al. found that the incidence of metoclopramide-induced tardive dyskinesia was 8.4 per 1000 patients, with a confidence interval excluding the null value. However, this study did not evaluate the duration of metoclopramide use and the indication of metoclopramide use. Interestingly, this study found that the incidence of spontaneous dyskinesia was 28.7 per 1000 patients. This finding is of significant importance as this suggests that many patients with suspected metoclopramide-induced dyskinesia might in fact have spontaneous dyskinesia. Nonetheless, due to the lack of diagnostic criteria, this would be difficult to prove clinically [36].

A recent study utilizing the concept of real-world data with a large sample size based on insurance data and claims between 2011 and 2020, found that the incidence of metoclopramide-induced TD in GP patients is far lower than previously expected, 0.1% [37].

There have been no prospective studies to evaluate the incidence and accurate prevalence of metoclopramide-induced tardive dyskinesia. A review of the literature suggests that the true risk of tardive dyskinesia secondary to metoclopramide use is far lower than the currently suggested prevalence of 1–10%.

The mechanism of tardive dyskinesia remains poorly understood. A proposed mechanism of the initial hypersensitivity of D2 receptors occurs, followed by upregulation of the D2 receptors and resulting in increased disorganized dopaminergic effects. Imbalances between D1 and D2 receptor activity have also been hypothesized as metoclopramide and first-generation antipsychotics primarily block D2 receptors and have a higher incidence of tardive dyskinesia compared to second-generation antipsychotics, which primarily exert their effect through a D1 receptor blockade. Furthermore, chronic D2 blockade is thought to cause an increase in excitatory glutamate levels leading to the destruction of GABA-producing striatopallidal neurons [38].

Certain subpopulations were found at greater risk of developing metoclopramide-induced tardive dyskinesia such as those of older age, females, diabetics, and those with concomitant psychiatric disorders or concurrent use of antipsychotics. This brings a dilemma to physicians as metoclopramide is the only FDA-approved medication for diabetic GP [32]. A study conducted in the UK found that the relative risk of developing extrapyramidal side effects was 1.8 in females compared to males, which was a statistically significant difference [20]. The effect of age on the risk of extrapyramidal symptoms appears to be more complex, with pediatric populations at a higher risk of dystonia whereas elderly patients have a higher risk of tardive dyskinesia.

The risk of developing tardive dyskinesia with metoclopramide use is linked to the duration of use (>12 weeks), dose (higher risk in doses >10 mg per dose or 30 mg daily), and frequency (>3 times a day) of administration [39]. Tardive dyskinesia is a hyperkinetic disorder presenting with a variety of symptoms such as chorea, stereotyped movement

patterns, involuntary purposeless movements or postures (e.g., lip smacking), and athetosis. The diagnosis requires the emergence of symptoms after >12 weeks of medication use in addition to the persistence of symptoms for at least 1 month following medication discontinuation [40]. The natural history of the disease was thought to be irreversible, however, up to 40% of patients have improvement in symptoms following early diagnosis and management. Nonetheless, the improvement in symptoms is a slow process and can last up to 3 years following medication discontinuation. The primary treatment of tardive dyskinesia is early recognition of the disease and immediate medication discontinuation which increases the potential for improvement or recovery. It should be noted, however, that drug discontinuation in itself can cause withdrawal-induced dyskinesia which is generally self-resolving over several weeks. Drug discontinuation or dose reduction after the development of tardive dyskinesia has unclear efficacy as some studies showed no difference in tardive dyskinesia symptoms in contrast to other studies where some improvement was noted [41,42]. In patients with moderate to severe symptoms and/or impaired quality of life despite medication discontinuation, symptomatic therapy can be initiated. Vesicular monoamine transporter type 2 inhibitors such as tetrabenazine, deutetabenazine, or valbenazine have been approved by the FDA in 2017 for tardive dyskinesia management. In addition, benzodiazepines (clonazepam) showed improvement in mild tardive dyskinesia symptoms, however, they are unlikely helpful in severe tardive dyskinesia [43]. In refractory cases, a movement disorder specialist consultation is required for possible evaluation of deep brain stimulation. A systematic review by Mentzel et al. in 2012 included a total of 50 patients and showed that 77.5% of patients noted improvement in tardive dyskinesia symptoms following deep brain stimulation for a period of at least 3 months [44]. Furthermore, Ginkgo biloba extract was evaluated in a randomized double-blinded clinical trial in 2011 among schizophrenic patients and showed significant improvement in tardive dyskinesia symptoms at 12 weeks [45].

Modalities to decrease the risk of tardive dyskinesia based on expert opinion include a clear indication of metoclopramide use, avoiding use for >12 weeks, the use of the lowest effective dose possible, continuous monitoring for extrapyramidal symptoms, and patient-centered care. Since diabetic gastroparesis is a chronic entity, treatment beyond 12 weeks will be usually required. Hence, we recommend the following strategies to potentially prevent extrapyramidal symptoms in patients requiring >12 weeks of treatment which include: drug holidays (time periods of 2–4 weeks is our suggestion), use of medication on an as-needed basis, use of lowest effective dose possible, close monitoring of renal function while on treatment and dose adjustment accordingly, avoiding the concurrent use of anti-dopaminergic medications (e.g., antipsychotics), and careful examination of the patient's medication list to assess for potential medication interactions. Medicolegal aspects should be considered, and, besides the aforementioned modalities, patients should be informed prior to initiation of metoclopramide of the possible adverse events with clear documentation in patients' charts.

Other notable adverse effects include hyperprolactinemia and mood disorders such as depression or psychosis [15].

6.5. Alternative Gastroparesis Treatment Options

With the advancement and expansion of the medical literature, treatment modalities for GP have expanded, albeit with limited efficacy, and they include dietary modifications, adequate hydration, optimized glycemic control in diabetics, prokinetics, antidepressants, and electric stimulators. Dietary modifications are considered the first line in patients with mild GP, and low-fat and non-digestible fiber-containing diets have also been shown to improve symptom scores in patients with GP [46]. Adequate hydration and electrolyte supplementation are crucial in gastroparesis patients due to electrolyte imbalances secondary to persistent vomiting. Glycemic control in diabetics is of the utmost importance as hyperglycemia is associated with decreased gastric emptying and the opposite is also true, where hypoglycemia increases the rate of gastric emptying. The effect of glucose in

patients with diabetic GP is more complex secondary to pre-existing neuronal damage and the unpredictable postprandial glucose levels in patients with diabetic GP [47].

Domperidone is a D2 receptor antagonist and possesses a similar mechanism of action to metoclopramide, however, is not known to cause significant extrapyramidal symptoms. A prospective study by Parkman et al. in 2016 evaluated the effect of domperidone on symptom scores and the prevalence of reported side effects in GP patients over a 2–3 month follow-up period. Movement-related adverse events were minimal as only 2 out of 115 patients developed movement-related adverse events (tremor and akathisia), both of which were mild and did not require medication discontinuation. This study, however, did not have a prolonged follow-up period to assess for further movement-related adverse events [48]. Domperidone is contraindicated in patients with a prolonged corrected QT interval due to the risk of cardiac arrhythmias. A double-blinded randomized clinical trial by Barnett et al. in 1999 compared the efficacy of metoclopramide and domperidone on GP symptoms. The study concluded that both medications were equally effective in treating GP symptoms, with a decreased incidence of adverse events in patients receiving domperidone [49]. Large-scale studies evaluating domperidone are lacking, thus, domperidone is FDA-approved in the United States only through FDA IND application for GP.

Macrolides have proven to increase fundic contractility and improve gastric emptying through their motilin receptor agonist activity. Intravenous erythromycin showed the most significant improvement in gastric emptying rates and was found to decrease pyloric sphincter tone through the activation of cholinergic receptors. Oral erythromycin improves GP symptom scores, however, tachyphylaxis occurs beyond 4 weeks of continuous use due to motilin receptor downregulation [46]. Caution must be practiced with macrolides due to their QT-prolonging effects and drug interactions secondary to CYP3A4 inhibition.

Prucalopride was the first selective 5HT₄ receptor agonist found in clinical practice. It is used in some countries to treat chronic constipation in patients who have failed with other laxatives, however, its use in GP has not been well studied and remains of limited utility [1].

Other 5HT₄ receptor agonists such as cisapride, tegaserod, and mosapride are prokinetic medications with potential benefits in GP. Cisapride was withdrawn from the US market due to an increased incidence of cardiac arrhythmias. Tegaserod is an approved prokinetic for chronic constipation and constipation-predominant irritable bowel syndrome that increases small bowel and proximal colon motility. Nonetheless, in a study of 163 patients, it was found that gastric emptying rates were increased at higher doses. The effect on the GP symptom score was not evaluated. In addition, unlike cisapride, tegaserod has no effect on the QT interval. Tegaserod has been withdrawn from the United States market as of June 2022.

Symptomatic therapy with anti-emetics can be helpful for the treatment of nausea and vomiting, with the most commonly used medications in gastroparesis patients being antihistamines (e.g., promethazine) and 5HT₃ antagonists (e.g., ondansetron).

Patients with refractory symptoms occasionally require percutaneous endoscopic gastrostomy (PEG) tube placement, jejunostomy tube placement, or, in severe cases, parenteral feeding. A weight loss of 10% body weight in a 3–6 month period or repeated hospitalizations with unremitting symptoms are some of the indications for PEG or jejunostomy tube placement [50].

For patients not responding to or unable to tolerate medical therapies, the final potential solution is surgical modalities such as pyloroplasty and gastric electric stimulator implantation. A recent double-blinded study by McCallum et al. showed up to a 75% symptom improvement over 4 years in gastroparesis patients who underwent the aforementioned interventions [51]. Endoscopic procedures such as endoscopic pyloromyotomy are also reserved for refractory GP but the long-term outcomes have not been well studied.

7. Conclusions

Metoclopramide has long been a cornerstone in the management of GP due to its prokinetic effect along with the clinical improvement in patients' symptom scores. The previously reported risk of tardive dyskinesia (1–10%) is likely overestimated as a thorough review of the current literature suggests a much lower incidence of metoclopramide-induced tardive dyskinesia. Newer formulations of metoclopramide, such as the intranasal form, can achieve symptom control more reliably by having guaranteed systemic absorption and, hence, could lower the dose required to achieve symptom control. In addition, it is important to note that it is always crucial to discuss, inform, and educate the patient about the potential for tardive dyskinesia, which could then lead to earlier detection and an improvement in long-term clinical outcomes.

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