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Mirtazapine for gastrointestinal side effects of glucagon-like peptide-1 receptor agonist therapy in older adults

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Objective. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) play a role in management of type 2 diabetes (T2D) and obesity by promoting glycemic control and weight reduction. Beyond these benefits, GLP-1 RAs have demonstrated positive effects on cardiovascular, renal, and neurological health, with emerging evidence supporting their therapeutic potential in conditions such as chronic kidney disease, asthma, obstructive sleep apnea, Parkinson's disease, and Alzheimer's disease. However, their widespread clinical use is often hindered by gastrointestinal side effects including nausea, anorexia, vomiting, and diarrhea that limit adherence and dose titration. Effective management of these adverse effects is essential to optimize treatment outcomes and maintain long-term therapy.

Case report. A 72-year-old woman with a history of cognitive impairment, T2D, atrial fibrillation, obesity, and mood disorders presented with persistent gastrointestinal symptoms while receiving semaglutide. Dose escalation was restricted due to severe nausea, vomiting, and diarrhea, which markedly affected her quality of life. To manage these symptoms, mirtazapine was initiated. Following its introduction, the patient reported significant improvement in gastrointestinal tolerance enabling continued semaglutide therapy and successful dose advancement. Additional benefits included enhanced mood, better sleep, and overall well-being. No adverse effects related to mirtazapine were observed throughout the treatment.

Conclusion. This case suggests that mirtazapine may be beneficial in mitigating GLP-1 RA-induced gastrointestinal side effects, thereby improving adherence and therapeutic efficacy. Further research is needed to evaluate the safety, mechanism, and generalizability of this approach in broader clinical practice.

Keywords: GLP-1 receptor agonists, mirtazapine, gastrointestinal side effects, diabetes, older adults, cognitive impairment

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are integral in managing type 2 diabetes (T2D) and obesity offering benefits beyond glycemic control and weight loss. Notably, these agents reduce cardiovascular risk, as demonstrated by clinical trials showing significant reductions in major adverse cardiovascular events including myocardial infarction and stroke (Marso et al. 2016). A meta-analysis further confirmed that GLP-1 RAs lower these events by 14% in adults over 65 years underscoring their importance for older populations (Karagiannis et al. 2021). Additionally, GLP-1 RAs have been shown to slow chronic kidney disease progression by reducing albuminuria, likely through improvements in endothelial function and reductions in inflammation (Heerspink et al. 2023).

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Beyond cardiovascular and renal benefits, GLP-1 RAs may have neuroprotective properties and beneficial effects on obstructive sleep apnea and asthma (Kanwar et al. 2022; Sultana et al. 2022; Russjan 2024; Anderer 2025; Lee et al. 2025). Preclinical studies have suggested that these agents reduce neuroinflammation and oxidative stress, mechanisms implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's (Talbot and Wang 2014; Zhang et al. 2019; Meissner et al. 2024; Cummings et al. 2025. These agents have been shown to reduce alpha-synuclein accumulation in Parkinson's disease models and mitigate amyloid-beta and tau pathology in Alzheimer's disease models suggesting a broader therapeutic role. However, despite these advantages, the use of GLP-1 RAs is often hindered by gastrointestinal side effects, including nausea, vomiting, and diarrhea, which impact adherence particularly in older adults with multiple comorbidities. A review found that gastrointestinal adverse events occur in 40% to 70% of patients leading to discontinuation in up to 12% of cases (Gorgojo-Martinez et al. 2022). Effective strategies to mitigate these adverse effects are crucial for optimizing treatment benefits.

Mirtazapine, an atypical antidepressant, may help manage these side effects through its antagonism of 5-HT3 receptors, which are involved in emetic signaling (Jilani et al. 2024). Additional evidence suggests its role in managing diarrhea-predominant irritable bowel syndrome and gastrointestinal symptoms of opioid withdrawal (Lalani et al.2023; Khan et al. 2024). Its H1 histamine receptor blockade also provides sedative effects that may reduce nausea-related distress and improve sleep. These properties position mirtazapine as a potential adjunct therapy to enhance tolerance and adherence to GLP-1 RA therapy. Beyond its antiemetic effects, mirtazapine is particularly suited for older adults. Unlike tricyclic antidepressants and certain selective serotonin reuptake inhibitors (such as paroxetine), it has minimal anticholinergic activity reducing the risk of delirium, urinary retention, and orthostatic hypotension (Garakani et al. 2020). Additionally, its appetite-stimulating effects can benefit frail older adults or those with unintentional weight loss. These combined benefits make mirtazapine a valuable option for managing GLP-1 RA-induced gastrointestinal intolerance in older patients. This case report explores the potential use of mirtazapine to alleviate GLP-1 RA side effects in a patient with coexisting mood disorder and multimorbidity.

Case report

A 72-year-old Caucasian female with a history of T2D, obesity, cognitive impairment (Functional Assessment Staging Tool [FAST] stage 3), atrial fibrillation, obstructive sleep apnea, hypertension, osteoarthritis, and mood disorders presented to the geriatric clinic for a routine evaluation. Her elevated weight (BMI 35.24 kg/m^2) was contributing to chronic joint pain and limiting mobility. To address both weight management and glycemic control (HbA1C 6.6%), semaglutide was initiated. She tolerated a weekly dose of 0.25 mg of semaglutide for approximately 1.5 years without any adverse events. However, upon dose escalation to 0.5 mg weekly, she developed persistent gastrointestinal side effects including nausea, vomiting, and diarrhea, which significantly affected her daily activities and willingness to continue treatment. The patient reported that these gastrointestinal symptoms confined her to her home preventing participation in recreational activities and significantly increasing her stress. To alleviate these symptoms while maintaining semaglutide treatment, mirtazapine was introduced at a nightly dose of 15 mg. Within one week, she reported complete resolution of her gastrointestinal symptoms. Additionally, she noted improvements in mood, sleep quality, and overall well-being. She was able to resume social activities and continue semaglutide without further gastrointestinal issues. After five months on this regimen, she maintained a steady weight loss (BMI 30.2 kg/m^2) and well-controlled diabetes (HbA1C 5.0%). She reported significant symptom relief and an improvement in her quality of life following the addition of mirtazapine.

Ethics approval. This case report was reviewed by the University of Texas Medical Branch (UTMB) Institutional Review Board (IRB) and was determined to be exempt from IRB review. An official acknowledgment letter of exemption was provided by the UTMB IRB committee.

Discussion

Gastrointestinal side effects are a common reason for discontinuing GLP-1 RA therapy, particularly among older adults. Symptoms such as nausea, vomiting, and delayed gastric emptying can significantly affect adherence and reduce the therapeutic effectiveness of these medications. Recent studies have reported real-world discontinuation rates for GLP-1 RAs ranging from 50% to 75% within 12 months of initiation (Khan et al. 2025). A large

cohort study also suggests that 46.5% of patients with T2D and up to 64.8% of those without diabetes discontinue GLP-1 RA therapy within one year with adverse gastrointestinal events being a leading factor (Rodriguez et al. 2025). While nausea and vomiting are the most frequently reported gastrointestinal side effects, more serious adverse events, such as gastroparesis and acute pancreatitis, though less common, have also been documented (Sodhi et al. 2023; Do et al. 2024). Among available GLP-1 RAs, semaglutide is notably associated with a higher incidence of gastrointestinal side effects compared to liraglutide and dulaglutide possibly due to its prolonged half-life and increased receptor potency (Liu et al. 2022). Similarly, tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, has demonstrated potent metabolic benefits, but may exhibit gastrointestinal symptoms comparable to those observed with semaglutide (Rodriguez et al. 2024). Understanding the nuanced differences in gastrointestinal tolerability between these agents is crucial, especially in older adults, to maximize therapeutic adherence and minimize risks.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, has a unique pharmacologic profile that makes it especially useful in managing GLP-1 RA-induced gastrointestinal side effects while also addressing comorbid insomnia and mood disorders. The drug antagonizes central presynaptic α_2-adrenergic autoreceptors and heteroreceptors enhancing the release of norepinephrine and serotonin. Additionally, mirtazapine blocks multiple serotonin receptors-including 5-HT2A, 5-HT2C, and most importantly for its antiemetic effect, 5-HT3. By blocking 5-HT3 receptors in both the chemoreceptor trigger zone and the gastrointestinal tract, mirtazapine helps reduce nausea and vomiting. Furthermore, its potent antihistaminergic effects via H1 blockade contribute to its sedative properties, potentially relieving distress from gastrointestinal symptoms (Jilani et al. 2024).

Pharmacokinetically, mirtazapine is rapidly absorbed after oral administration, reaching peak plasma concentrations approximately two hours post-ingestion (Sagiraju et al. 2024). Its clinical effects depend on the dose: lower doses (7.5–15 mg) primarily affect H1 and 5-HT3 receptors enhancing sedation and antiemetic effects, while higher doses (30–45 mg) more strongly engage α_2-adrenergic and noradrenergic pathways improving energy, appetite, and mood (Hassanein et al. 2024). Alternative formulations, such as sublingual and orally disintegrating tablets, have shown faster onset and higher bioavailability, although data remain limited. Clinically, mirtazapine has shown effectiveness beyond depression and insomnia serving as an off-label antiemetic for chemotherapy-induced nausea and vomiting, as well as cases of hyperemesis gravidarum. Further highlighting its broader utility in managing difficult-to-treat nausea when conventional agents fail (Raji 2005; Aktemur et al. 2024). Recent evidence also suggests improved adherence and metabolic outcomes among patients receiving GLP-1 RAs when antiemetic therapies including mirtazapine are concurrently used (Hassanein et al. 2024).

In this case, mirtazapine enabled the patient to continue semaglutide therapy without further gastrointestinal distress. Its additional benefits including improved sleep and mood stabilization further enhanced the patient's overall well-being. Given its effectiveness in this case, mirtazapine may serve as a valuable adjunctive therapy for patients experiencing GLP-1 RA-induced gastrointestinal side effects. Future studies should investigate its role in broader clinical settings to establish standardized treatment recommendations.

This case illustrates the potential role of mirtazapine in alleviating GLP-1 RA-induced gastrointestinal side effects, thereby improving adherence and optimizing therapeutic outcomes. Mirtazapine's antiemetic and appetite-enhancing properties make it a compelling adjunct therapy, especially for older adults who may be more susceptible to medication intolerance. Further research is warranted to explore its broader applicability in clinical practice.

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Conflict of interest: *The authors declare that they have no competing interests.*

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