Role of Glucagon-Like Peptide-1 Receptor Agonists in Managing Antipsychotic Induced Weight Gain causing Non-Compliance in Bipolar Disorder Patients: A Case Series.

Abstract

Bipolar disorder is one of the most common mental health disorders worldwide. Antipsychotics are highly used agents in the management of this mood disorder. One of the most common and distressing side effects of these medications is weight gain. Weight gain not only creates metabolic impairment but also causes many patients to discontinue antipsychotic treatment to avoid the side effect of weight gain, leading to relapses and hospitalisation. Every other exacerbation of the disease makes the next one more likely, which is why early interventions have a key role in disease management. Although GLP-1 agonists have been used to promote weight loss in patients with obesity and diabetes, their use as a preventive strategy in patients at high risk for non-compliance to antipsychotics due to weight gain has not been widely adopted in clinical practice. We present a case series of three adult female patients with bipolar disorder treated with antipsychotics who experienced relapses requiring hospitalisation due to non-with compliance due to antipsychotic-induced weight gain.

***Keywords** : GLP-1 Receptor Agonist, Antipsychotic, Bipolar Disorder, Non-adherence, Weight Gain*

Introduction

Psychiatric disorders are highly prevalent, distressing conditions with multifaceted challenges that affect individuals on a worldwide scale (Le et al., 2021). More than one percent of the global population is diagnosed with bipolar disorder (BD), which can significantly burden patients with chronic socioeconomic, medical, familial, etc. issues (Grande et al., 2016). Recurrent mood swings that disrupt functionality are characteristic of BD type 1 and 2, with BD type 1 associated with more severe manic episodes than its hypomanic counterpart (DSM-5 TR, 2022). First-line management of BD typically involves the use of mood stabilizers and

antipsychotics (Yıldız et al., 2015). Some reviews have reported that antipsychotics demonstrate superior efficiency to mood stabilizers because of their faster onset of action and higher response rates (Yıldız et al., 2015; Cipriani et al., 2011).

Antipsychotics are widely utilized in psychiatry. Besides their on-label use for BD, schizophrenia; antipsychotics have been implemented in treatment regimens to variable disorders (Stogios et al., 2021). A comprehensive UK study reported that 68.7% of patients with severe mental illnesses used antipsychotics at least once in their lifetime, and the usage of antipsychotics has increased over the past 20 years (Richards-Belle et al., 2024). Despite their efficacy in the treatment of mania with or without psychosis, antipsychotics have several side effects (Bobo et al., 2017; Kaar et al., 2020). Weight gain is the most common side effect of antipsychotics, followed by extrapyramidal symptoms and sedation (Lieberman et al., 2005). Up to 74 percent percent of patients taking an antipsychotic state weight gain is the most distressing side effect; for patients with BD, the propensity to gain weight compounded with mood stabilizers only exacerbates the troublesome struggle with weight management (Fakhoury et al., 2001; Chue & Cheung, 2004). Weight gain in BD generally relates to microvascular and macrovascular complications, consequently leading to a reduction in quality of life and psychological well-being (Chue & Cheung, 2004; Schuster & Duvuuri, 2002).

Control of side effects plays a key role in pharmaceutical management of BD because side effects can lead to non- or poor- adherence, eventually leading to relapses and hospitalizations (Chue & Cheung, 2004; Chakrabarti, 2016). However, an alternative drug or reduction in dose of antipsychotics is attractive but remains controversial because of potential risk of relapse (Chue & Cheung, 2004; Stroup & Gray, 2018). Besides changes in psychiatric medications, augmenting a pharmacological agent to treatment regimens may be a beneficial and safe option for individuals with BD.

Of the existing pharmacological interventions, metformin is recommended for the management of obesity in the general population (Knowler et al., 2002). Several guidelines have been established for the use of metformin in the prevention of antipsychotic-induced weight gain (Carolan et al., 2025). Metformin has shown effectiveness in specific groups: 1. patients on high-risk antipsychotics, 2. patients aged 10–25 years or those with one or more cardiometabolic risk factors on medium-risk antipsychotics, and 3. patients who show over a three percent increase from baseline body weight during the first year of treatment (Carolan et al., 2025). Metformin's

long-established safety profile has validated its use in clinical settings (Carolan et al., 2025). However, only seventeen percent of individuals in a randomized clinical trial of metformin lost greater than five percent of their body weight (Jarskog et al., 2013). Such results have led researchers and healthcare providers to consider alternative medications for weight loss, and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have received much attention for their weight loss capabilities.

GLP-1RAs prescription rates have risen significantly in recent years because of their highly-effective ability to manage obesity (Li et al., 2024; Wilding et al., 2021). Approximately 86 percent of obese patients achieved weight reductions of five percent or more when taking GLP-1RAs (Wilding et al., 2021). Although there are few established guidelines for the use of these medications to target antipsychotic-induced weight gain, GLP-1RAs have significantly reduced body mass index, waist circumference, and HbA1C levels in obese antipsychotic-treated patients (Patoulias et al., 2023).

We present three cases of patients with bipolar disorder, antipsychotic medications were used for control of their manic symptoms, and weight gained was significant and did not respond to either change in the specific antipsychotic used, nor with metformin or lifestyle recommendations but with the used GLP-1 receptor agonist medications, which were well tolerated and effective in achieving consistent and significant weight loss.

Case Series

Case 1:

We present an 18-year-old female patient with no personal history of psychiatric or medical conditions, but with a family history of bipolar disorder in her father. The patient was diagnosed with BD type 1 two years ago after experiencing a severe manic episode, in which she presented a marked elevated mood concurrent with barely three hours of sleep each night for five days. At that time, her Young Mania Rating Scale (YMRS) was 35 points, with a score of eight in both elevated mood and sleep disturbance.

Olanzapine 10 mg QD was prescribed along with lithium 600 mg QD, achieving remission of the episode. By the end of the fourth day of treatment, her YMRS had decreased to

five points, warranting discharge from the hospital. Her home treatment regimen consisted of olanzapine 5 mg QD and lithium 600 mg QD. At that time, her weight was 120 pounds.

During the next ten months, she remained free from manic and depressive symptoms and strictly complied with her medication regimen. However, the patient gained 48 pounds of weight during the treatment period and abruptly discontinued her medications. Within a week of the patient stopping her medication, she started reporting chest discomfort, anxiety, and trouble sleeping. She was hospitalized ten days later with a manic episode presenting as significant agitation, hyperactivity, delusional ideation, reduced need for sleep, and lack of insight. Her YMRS score was a score of 32. Aripiprazole 400 mg QM injection was then started in order to prevent abrupt discontinuation of the medication. By the end of the first week of the new treatment method, the patient YMRS was less than five points (thus, she was discharged).

Four months after the second hospitalization, the patient was still free of manic and depressive symptoms, but her weight increased by 40 pounds compared to her weight at the time of her hospitalization. Aripiprazole was replaced by lamotrigine 100 mg QD, Cariprazine HCl 1.5 mg QD and lifestyle changes paired with 500 mg metformin QD were added to her treatment plan. The patient remained free of symptoms for the next four months but gained an additional 22 pounds, making her total weight 230 pounds.

Tirazepatide 2.5 mg/0.5 ml QW SC injection was added and the patient was reevaluated six weeks after. The patient did not endorse any depressive or manic symptoms, adhered to her medication regimen, and reported decreased appetite resulting in 20 pounds lost. No significant adverse effects were reported.

Case 2:

A 32-year-old female patient with no personal history of psychiatric/medical conditions but a family history of bipolar disorder I as seen in her brother. Two years ago, her diagnosis was confirmed after the patient experienced a manic episode characterized by delusions of grandeur, reduced need for sleep, irritability, and a YMRS score of 35. This episode required hospitalization, and lithium 600 mg QD plus injectable aripiprazole 675 mg QM were started. She responded almost immediately and was discharged on day five with a YMRS score of 5, weighing 140 pounds at this point.

For the next eight months, no symptoms of mania or depression were reported (YRMS: 0), but the patient was significantly distressed by her weight gain of 50 pounds. Aripiprazole injections were discontinued and cariprazine 1.5 mg QD with metformin 500 mg QD were started. The new regimen was well-tolerated and the patient remained free of symptoms. Her weight was steady at 190 pounds.

Two months after the beginning of the new treatment, she had gained another 15 pounds despite excellent control of her BD symptoms. Cariprazine was then suspended and replaced with lamotrigine 400 mg QD, augmented with olanzapine-samidorphan 10-10mg (Lybalvi). To address the issues with the patient's weight (which was 205 pounds at this point), semaglutide 2mg QW, a GLP-1 receptor agonist, was initiated. The patient was reevaluated after six weeks: both the manic and depressive symptoms were absent and her weight had dropped by 15 pounds. After another eight weeks of the new regimen, she remained free from any manic or depressive symptoms and lost an additional 15 pounds.

Case 3:

We present a 36-year-old female with a four-year history of bipolar disorder I, first diagnosed after a manic episode with severe agitation, hallucination, hypersexuality and marked increase in her energy levels. At the time of her manic episode, she scored a total of 34 points on the YMRS. She required hospitalization and was started on lithium 900 mg QD and lamotrigine 100 mg QD, which helped the patient remain free of manic and depressive symptoms (without side effects) for just under two years. However, 20 months after the initial hospitalization, the patient once again required psychiatric hospitalization to address a new episode of mania. She presented to the hospital scoring 30 points on the YMRS with marked sleep disturbance and significantly elevated mood. The patient's medication plan was discontinued to initiate olanzapine 2.5 mg QD with IM aripiprazole 960 mg QM. The manic episode was controlled within three days of implementing the new medications and the patient was discharged with instructions to continue the new regimen. At this point, she weighed 140 pounds and her YMRS score was three points.

Despite a lack of symptoms for two months and a YMRS score of five, the patient presented to the follow-up consultation with deep concerns regarding her recent 30 pound

increase in her weight (170 pounds). Olanzapine was then discontinued and the combination olanzapine-samidorphan (Lybalvi) was started.

For the next six months, no symptoms were present, but the patient reported gaining 20 more pounds. Metformin 500 mg QD was prescribed along with a reduction in the dose of aripiprazole, from 960 mg QM to 400 mg QM. Although the change in medication prevented excessive weight gain, the patient reported decreased sleeping, mild agitation, and anxiety one month later at her aripiprazole injection follow-up. Further, her YMRS score increased to 14 points, up from a previous score of three just one month ago. Her aripiprazole dose was thus changed to 1062 mg QM to address these symptoms. Her weight was recorded to be 190 pounds at the start of the new treatment regimen.

By the end of the second month with the new treatment, the patient was extremely distressed since she had gained 30 pounds and now weighed 210 pounds. The patient reported an almost uncontrollable appetite, but her depressive and manic symptoms remained absent. IM Semaglutide, a GLP-1 receptor agonist, was initiated at a dose of 0.5 mg QW. At the follow-up appointment two months later, the patient had lost 20 pounds (a total weight of 190 pounds). After another two months, she had lost an additional 15 pounds (now weighing 175 pounds) with a significant decrease in appetite and no adverse events reported.

Discussion

This case series presents three young-adult female patients diagnosed with bipolar disorder who exhibited excessive weight gain throughout medication regimens. In all of them and in correspondence with several studies (Khandker et al., 2023;De et al., 2025), the distress of extreme weight gain led to discontinuation of treatment, relapses, and hospitalizations. Despite changes in doses and type of medication, augmenting metformin, lifestyle changes to promote weight loss, no progress was seen in any of them while under treatment with antipsychotics. Compliance to their respective treatment regimes was restored with initiation of GLP-1RAs, resulting in significant and consistent weight loss. Following up over the course of 2 years showed that weight gain is a primary driver in medication nonadherence, which, as seen in these patients, has severe medical and functional consequences. GLP-1RAs showed no side effects and

led to a marked improvement of medication adherence and consequently to control of the symptoms related to bipolar disorder.

Medication side effects, lack of insight into the illness, cognitive dysfunction, regimen complexity, and substance use are all factors that may result in spontaneous discontinuation of treatment regimens, especially for individuals with BD (Loots et al., 2021). Approximately seven out of ten patients with BD are overweight or obese and are looking for management methods (DE Hert et al., 2011). Younger BD patients, especially females, are at increased risk of antipsychotics-induced weight gain (even more so if the patient is already taking a mood stabilizer, antidepressant, or benzodiazepine) (Castellani et al., 2020 & Milano et al., 2013). In a randomized clinical trial, clozapine-induced weight gain was reported in 5.5% of females compared to 1.3% in male counterparts (Lau et al., 2016). Furthermore, patients with BD display more body image concerns than healthy controls (Pan et al., 2019).These outcomes can place young-adult female patients, the group at the highest risk of a BD diagnosis, in more vulnerable positions for noncompliance because of antipsychotic-induced weight gain (Oliva et al., 2024).

In BD, one in two patients is nonadherent to therapies (Loot et al., 2021). The most significant consequences of nonadherence are increased rates of hospitalization and relapse (Loot et al., 2021). Nonadherent patients are at a 3.7 times greater risk of relapse than in adherent patients; this risk increases five-fold if patients do spontaneously discontinue their medications (Loot et al., 2021). Female sex is a risk factor for hospitalization (Fellinger et al., 2018). The effects of mania in the brain include dilation of the ventricles and reduction in brain tissue density (Coffman & Nasrallah, 1985). Every acute exacerbation of the disease,being a manic, hypomanic or depressive episode, increases the risk of another crisis occurring further in time; therefore, early interventions have a key role in preventing progression (Post et al., 1992). These outcomes not only affect cognitive functions but also lead to a substantial escalation in healthcare costs (Bessonova et al., 2020). For young adult patients, every intervention that aims to save mental well-being is cost-saving. (Le et al., 2021; GBD, 2019).

Weight gain is both important in terms of antipsychotic-adherence and metabolic homeostasis (Noubia et al., 2025). Long term dysglycemia can result with micro- and macrovascular complications (e.g., neuropathy, coronary artery disease, stroke, myocardial infarction) (Schuste & Duvuuri., 2002). Because of the early-onset use of weight-gaining

medication, metabolic syndrome and complications of dysglycemia emerge at earlier ages for the psychiatric patient population (Grande et al., 2016). These factors contribute to increased severity of prognosis and rises in mortality rate (Vancampfort et al., 2015 & Noubiap et al., 2025; Doane et al., 2023).

Metabolic syndrome prevalence has increased over the past 25 years and is more common in females than in males (Noubiap et al., 2025). A comprehensive meta-analysis indicated 32 percent of psychiatric patients report metabolic symptoms, which is nearly fifty percent higher than the general population (Vancampfort et al., 2015).

Weight gain is one of the most common causes of medication nonadherence. It entails irreversible complications, and among individuals that take antipsychotic medications, females are far more vulnerable to weight gain than males (Milano et al., 2013). Thus, early interventions are critical for avoiding serious health consequences related to excessive weight. For the management of antipsychotic-induced weight gain, some guidelines have suggested pharmacological agent changes or dose reductions (Chue & Cheung, 2004). However, due to the high risk of relapse and hospitalization, they are no longer widely used treatment methods (Stroup & Gray, 2018).

In the general population, the primary medication used for weight reduction is metformin, which is regarded as a safe and effective drug despite the lack of efficacy seen in the patients (Knowler et al., 2002). Even though some national guidelines recommend metformin for antipsychotic-induced weight gain, there is conflicting evidence reporting limited/no effects or complete non-response to this type of treatment (Prasad et al., 2023; Pedersen et al., 2025; Jarskog et al., 2013). Notwithstanding the several interventions that currently exist, glycemic control in patients on antipsychotics remains poor (Wani et al., 2015). In a prospective analysis, 47.2 percent of patients developed new-onset impairment of glucose tolerance within 14 weeks of antipsychotic treatment (Wani et al., 2015). Furthermore, the use of GLP-1RAs has increased exponentially over the last 20 years, showing promising results for weight management in patients on antipsychotics (Li et al., 2024; Wilding et al., 2021).

Glucagon-like peptide-1 (GLP-1), also known as incretin, is normally produced in the gastrointestinal tract and plays a crucial role in metabolic homeostasis, euglycemia, and normolipidemia (Liu, 2024). It exerts its effects by activating downstream signaling across

various tissues and organs including the satiety centers to regulate food intake, pancreatic β cells to regulate insulin secretion, and adipocytes to increase the production of adiponectin (Liu, 2024). GLP-1 receptors are located in the cerebral cortex, thalamus, hypothalamus, substantia nigra, circumventricular organs, hippocampus, cerebellum, and brainstem nuclei (Khaity et al., 2023). GLP-1RAs activate cyclic adenosine monophosphate (cAMP) and provide neuroprotection, promote neuronal development, and reduce oxidative stress and neuroinflammation (Khaity et al., 2023). These receptors also stimulate neuroplasticity through the release of brain-derived neurotrophic factor, which can be highly beneficial in diseases resulting in cognitive impairment, such as BD (Khaity et al., 2023).

The effectiveness of GLP-1RAs in weight reduction has been proven in patients with obesity or type 2 diabetes mellitus (T2DM) because of its ability to significantly reduce diabetes-related complications (Wilding et al., 2021; Marso et al., 2016). GLP-1RAs have shown favorable side-effect profiles: the most common adverse events are gastrointestinal, such as nausea, diarrhea, vomiting, and constipation. These are typically mild to moderate in severity, transient, and often resolve without the discontinuation of the regimen (Wilding et al., 2021). Although there is limited data regarding GLP-1RA use in antipsychotic-induced weight gain, a meta-analysis supported their effectiveness in obese, antipsychotic-treated patients through reductions in body mass index (BMI), waist circumference, and HbA1c levels (Patoulias et al., 2023). Previous studies have reported that GLP-1RAs yield greater weight loss results than topiramate and metformin (Khaity et al., 2023). Furthermore, GLP-1RAs appear to be more effective in females (Marassi et al., 2025). In a 2025 clinical trial, more than 65 percent of females achieved a weight loss of 5 percent or more, compared to only 58 percent of males (Marassi et al.). Females showed 1.1 kg more weight loss than males, even when factors such as age and baseline weight were balanced (Marassi et al., 2025). We used this evidence to fortify our rationale to use this medication group on our patients, and the results corresponded with the literature we consulted.

Even when patients discontinue medication, weight gain induced by these drugs often persists (Doane et al., 2023). Obese patients are three times more likely to miss a dose of antipsychotics than non-obese individuals (Weiden et al., 2004). Thus, GLP-1RAs are beneficial

as a preventive measure against obesity despite this practice lacking wide use among the global medical community.

Understanding the limitations intrinsic to the design and nature of this study, further clinical trials are recommended to determine the optimal implementations of such medication regimens within this group of patients.

Further studies are required to understand the long term impact of GLP-1 agonists on compliance in patients with bipolar disorder. Moreover, careful consideration of antipsychotic associated weight gain is essential to identify patients at high risk of non compliance due to it and stop it before it happens. Early recognition and targeted intervention using GLP-1 agonists have the potential of improving overall clinical outcomes in patients with bipolar disorder

Ethical review and consent:

Formal ethical approval was not required for this study under local and institutional regulations. Written informed consent was obtained from the patient to publish this case.

Conflict of interest statement:

The authors have no conflicts of interest to disclose.

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Conclusions

In bipolar disorder, antipsychotic medications are regarded as effective and relatively safe treatments. Antipsychotic drugs aid in the control of acute episodes and in the prevention of recurrences, which can be triggered by significant physical, emotional, and social stressors. Though neurons are irreversibly lost with each manic or depressive episode, these medications can help preserve long-term brain health and survival.

The driving factor behind manic/depressive episode relapse in bipolar disorder is medication nonadherence, and weight gain is strongly related to the majority of antipsychotics

implemented in treatment regimens for this condition. Females are particularly susceptible to weight gain associated with antipsychotics. Changes in the doses, the medications itself, the addition of metformin, and choosing healthier lifestyle practices are implemented in management plans for this population on a frequent basis. GLP-1 receptor agonists are a group of medications commonly used to manage diabetes and obesity, and their effectiveness and safety have been reported consistently in literature. We suggest the use of GLP-1 receptor agonists as a preventive measure against excessive weight gain in patients with bipolar disorder taking antipsychotic medications. GLP-1RAs may be incredibly helpful in avoiding metabolic adverse effects and nonadherence among individuals with bipolar disorder prescribed antipsychotic drugs that are typically associated with weight gain.

Figures and Tables

Table 1

Medication regimen, GLP-1 use, and weight values across treatment

Treatment Phase	Patient 1	Patient 2	Patient 3
Psychiatric First Agent	Lithium 600 mg QD	Lithium 600 mg QD	Lithium 600 mg QD
Psychiatric Second Agent	Olanzapine 5mg QD	Aripiprazole 675 mg/2.4 mL IM QM	Lamotrigine 100 mg QD
Psychiatric Third Agent	Aripiprazole 400 mg IM QM	Cariprazine 1.5 mg QD	
Psychiatric Current Regimen	Cariprazine HCl 1.5 mg QD + Lamotrigine 100 mg QD	Lamotrigine 400 mg QD + Olanzapine/Samidorphan 10/10 mg QW	Aripiprazole 1064 mg QM IM + Olanzapine/Samidorphan 10/10 mg QW
Metabolic First Agent	Metformin 500 mg QD	Metformin 500 mg QD	Metformin 500 mg QD
Metabolic Current Agent	Tirzepatide 2.5 mg/0.5 mL QW SC	Semaglutide (oral) 2 mg/3 mL SC	Semaglutide (oral) 2 mg/3 mL SC
Baseline Weight	~120 lbs	~140 lbs	~145 lbs
Peak Weight	~230 lbs	~205 lbs	~210 lbs
Weight reduction with GLP-1RAs / Duration	~20 lbs / 6w	~30 lbs / 14w	~35 lbs / 16w

Note. IM = intramuscular; SC = subcutaneous; GLP-1 = glucagon-like peptide-1 receptor agonist QD = once a day; QW = once a week; QM= once a month w= week. Weight values are estimated from clinical documentation and should be interpreted with caution.

Figures 1-3

Medication timelines and estimated weight trajectories for case series patients.

Figure 1: Medication timeline and weight trajectory of patient 1, including hospitalization and GLP-1 receptor agonist initiation

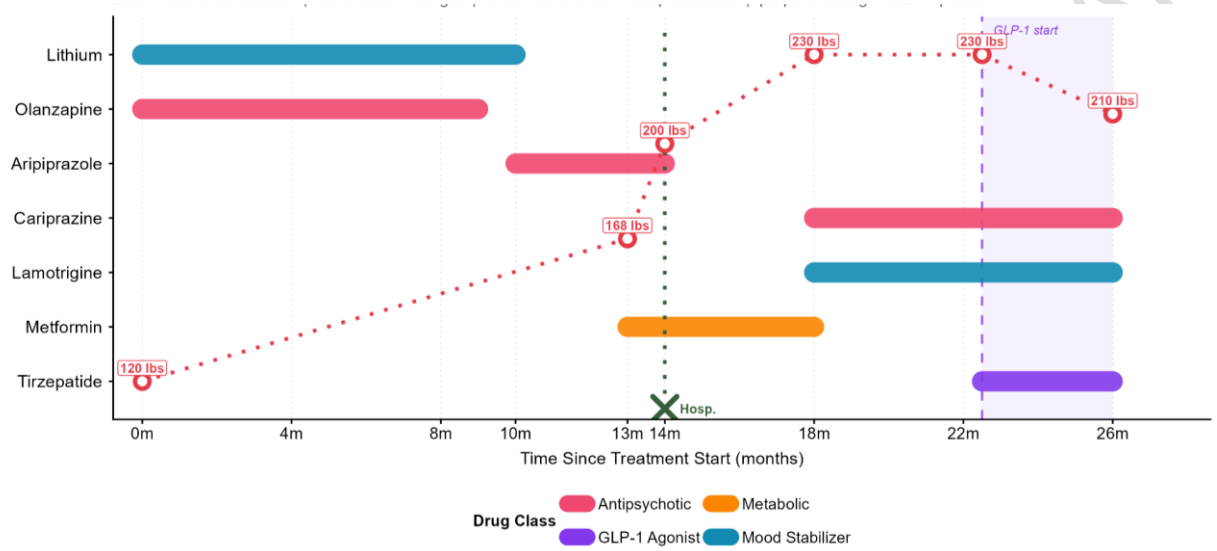


Figure 2: Medication timeline and weight trajectory of patient 2 including GLP-1 initiation

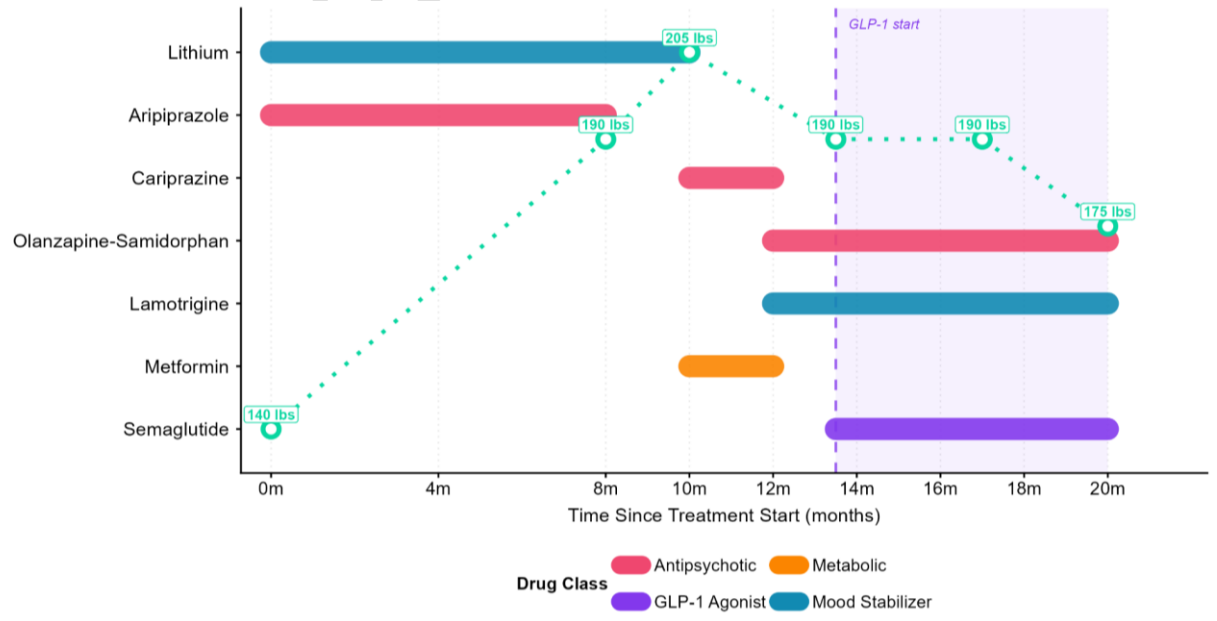
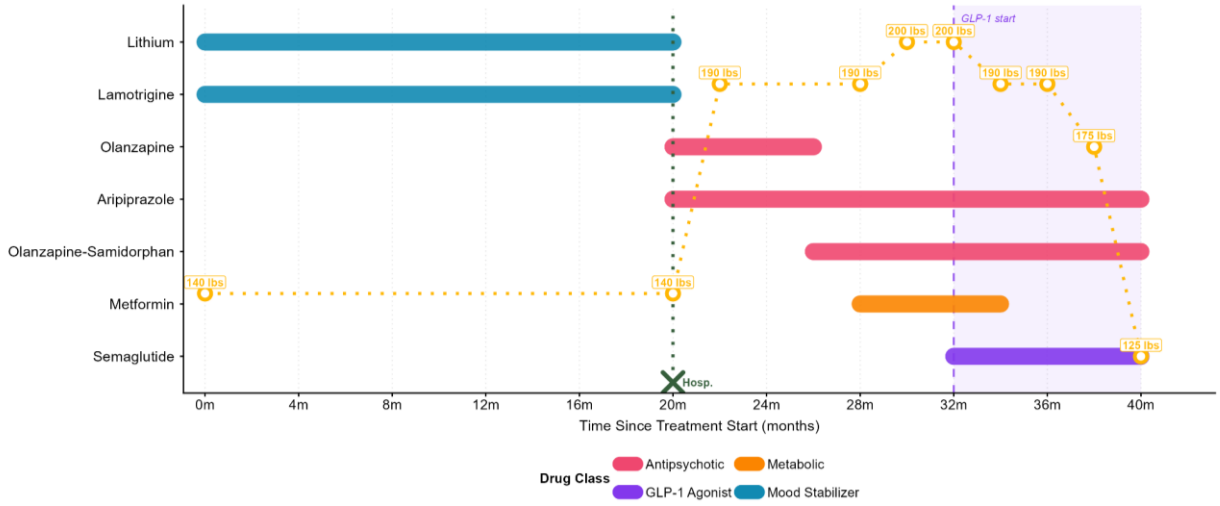


Figure 3: Medication timeline and weight trajectory of patient 3, including hospitalization and GLP-1 receptor agonist initiation



Note. Colored bars indicate active medication periods. Pink = antipsychotic, orange = metabolic agent, purple = GLP-1 receptor agonist; blue = mood stabilizer. Dotted line = weight in pounds; values are labeled at each documented timepoint. Green dotted vertical line = inpatient hospitalization. Purple shading = GLP-1 agonist treatment period.

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