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Article

Beyond Weight Loss: Tirzepatide and Eating Behaviors in Patients with Bipolar Disorder and Obesity

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Abstract: In bipolar disorder (BD) patients, obesity is highly prevalent and strongly influenced by maladaptive eating behaviors such as low cognitive restraint, high uncontrolled eating, and emotional eating. These traits contribute to weight gain and complicate treatment. In this context, interventions should not only aim to reduce excessive caloric intake and processed food consumption but also address the behavioral alimentation mechanisms underlying weight regulation. We conducted an observational study to evaluate the effects of tirzepatide, a dual GLP-1/GIP receptor agonist, in a real-world cohort of patients with bipolar disorder and obesity. Eating behaviors were assessed using the Three-Factor Eating Questionnaire. BMI changes were assessed. Safety and tolerability were evaluated using patient-reported outcomes and any treatment discontinuations. Significant improvements were observed across all subscales, with an increase in cognitive restraint and reductions in both uncontrolled eating and emotional eating. Tirzepatide was generally well tolerated, with only mild and transient adverse effects. These results suggest that tirzepatide may provide benefits extending beyond weight loss by enhancing cognitive restraint and reducing uncontrolled eating. In particular, the reduction in emotional eating may help break the cycle between affective symptoms and overeating, potentially lowering the risk of relapse and further metabolic deterioration. Although limited by a small sample size and an observational design, this study provides preliminary evidence that tirzepatide may address both biological and behavioral dimensions of obesity in bipolar disorder, warranting larger and longer-term investigations.

Keywords: tirzepatide; bipolar disorder; obesity; emotional eating; cognitive restraint; uncontrolled eating

1. Introduction

Obesity, when attributable to altered eating behaviors, is often the result of an imbalance between cognitive control over food intake and eating disinhibition [1,2]. This relationship is even more complicated, considering that eating is often influenced by emotional nuances that can alter food consumption, either increasing, reducing, or dysregulating it [3]. Thus, several aspects of eating behavior have been studied. First, cognitive restraint (CR), the ability to voluntarily limit food intake through conscious control, is typically employed to maintain a healthy body weight [4–7]. Cognitive restraint attempts to govern the more "instinctive" aspects of eating, such as uncontrolled eating (UE), the tendency to overeat without restraint in response to external stimuli or internal sensations of hunger [4–7]. Finally, as mentioned, emotions further color these aspects: in emotional eating (EE), people tend to eat in response to emotions, generally negative ones, such as sadness, anxiety, anger, or loneliness [4–7].

The balance described above is often disrupted in individuals with obesity, and this is especially true for patients vulnerable to impulsivity and loss of control, such as those with bipolar disorder (BD). Indeed, about 30–42% of

patients with BD meet criteria for obesity [8]. This association is relevant because it reduces quality of life, increases morbidity and mortality, raises the likelihood of relapse, and may also interfere with treatment adherence [9–11]. Beyond biological factors, such as inflammation [12], insulin resistance [13], alterations in gut microbiota [13], and pharmacological treatments side effects [11], it should be pointed out that the BD presentation itself includes features that contribute to weight gain and obesity: depressive phases are frequently associated with low activity, reduced self-care, and sometimes hyperphagia (especially in atypical depression), whereas hypo/manic phases are often marked by disinhibition and impulsivity, leading to irregular eating behaviors and metabolic alterations [14]. In addition, studies have demonstrated that BD patients usually have a sedentary lifestyle and low levels of physical activity, not only during depressive episodes but also during periods of euthymia [15]. Impulsivity and emotional dysregulation may play a role in this overlap [16], as cognitive control on overeating tends to be weaker. Even outside acute phases, BD patients tend to show higher impulsivity and poorer emotion regulation [17]. This is consistent with the frequent comorbidity between BD and eating disorders, especially of the binge/purge type [18,19]. Moreover, EE is more common in BD compared to healthy controls [20]. Managing this problem is not straightforward, also because many drugs prescribed for BD have increased appetite and weight gain as side effects.

Glucagon-like Peptide 1 (GLP-1) receptor agonists are now used worldwide not only in the treatment of diabetes but also for obesity and certain overweight conditions. These agents act directly on the gastrointestinal system by enhancing glucose-dependent insulin secretion, inhibiting glucagon, and reducing gastric emptying [21]. It is also important to emphasize their central nervous system effects: by acting primarily at the hypothalamic level, they reduce appetite [21]. Moreover, GLP-1 receptors are expressed in brain regions critical for the sensation of reward, such as the mesolimbic system [21,22], as well as in other areas involved in mood regulation and cognitive control (e.g., hypothalamus, hippocampus, amygdala, prefrontal cortex, and nucleus accumbens) [23]. Some of these compounds have already been used in psychiatric populations, for example, to counteract weight gain associated with antipsychotic treatment [24,25]. A randomized controlled trial on bipolar patients also demonstrated that liraglutide led not only to improvements in BMI and metabolic parameters, but also to reductions in hunger perception and binge-eating frequency [26]. However, evidence for their use in BD remains scarce. Preclinical studies further indicate that GLP-1 receptor agonists exert pleiotropic central effects, including anti-inflammatory and antioxidant actions, enhancement of mitochondrial and neurotrophic function and modulation of the hypothalamic-pituitary-adrenal (HPA) axis [23]. These mechanisms may underlie their potential benefits on mood and emotion regulation, beyond their well-established metabolic effects.

Tirzepatide, in particular, is not only a GLP-1 receptor agonist but also acts as a Gastric inhibitory polypeptide (GIP) receptor agonist. GIP binds to its class B G-protein-coupled receptor (GIPR) on pancreatic β-cells, adipocytes, and central nervous system sites, activating adenylate cyclase/cAMP and downstream signaling pathways that promote insulin secretion, adipogenesis, and modulation of appetite and reward-driven eating [27]. Preclinical and early clinical evidence show that dual GLP-1/GIP receptor agonism (for example tirzepatide) produces greater weight loss and improved glycemic control compared with GLP-1R agonism alone, suggesting a synergistic role of GIPR activation in regulating energy balance and food behaviour [28,29].

To the best of our knowledge, no studies to date have investigated the use of tirzepatide in patients with bipolar disorder. Our work aims to explore how tirzepatide may affect the regulation of food intake in this population, focusing in particular on the aforementioned aspect of eating behaviors: CR, UE, and EE—dimensions known to be altered in bipolar disorder and frequently associated with overweight and obesity. Secondary objectives include examining the impact of tirzepatide on BMI and evaluating its safety profile in bipolar patients.

2. Materials and Methods

This work represents a secondary analysis of data collected within the observational retrospective protocol LITHIUM THYROID (approved by the Institutional Review Board of the Comitato Etico Regione Toscana—Area Vasta Sud Est with the code 26967). The research was conducted in full compliance with the principles outlined in the Declaration of Helsinki and adhered to Good Clinical Practice (GCP) guidelines. Inclusion criteria of the LITHIUM THYROID protocol were (1) age ≥ 18 years without distinction of gender and ethnicity; (2) patients diagnosed with bipolar disorder according to DSM-5-TR and confirmed by clinical evaluation, who had been treated with lithium at some point during their clinical course; (3) signing of informed consent. Exclusion criteria included inability or unwillingness to provide data, diagnosis of Alzheimer's disease or other forms of dementia, cognitive impairment, moderate to severe intellectual disability, any other marked cognitive deficit, presence of organic brain disorders or uncontrolled medical conditions, and pregnancy or breastfeeding. In the LITHIUM THYROID protocol, 150 patients were enrolled. While the primary aim of that study was to examine thyroid function in patients with bipolar disorder previously or currently treated with lithium, here we examined

the subgroup of patients who also received tirzepatide for obesity, exploring its potential impact on eating behaviors (CR, UE, EE), body mass index, and tolerability.We considered 25 patients diagnosed with BD, treated with tirzepatide for obesity (BMI ≥ 30 kg/m^2) at the Department of Psychiatry of the University Hospital of Siena. Demographic and clinical data (such as age, sex, anthropometric measures, and pharmacological treatments) were extracted from clinical records.

Body weight and height were recorded at baseline and at the time of assessment, and BMI was calculated as weight (kg)/height^2 (m^2). Patients also completed the Three-Factor Eating Questionnaire Revised-18 (TFEQ-R18) at the time of assessment, rating both their current status (Post) and retrospectively their status before starting tirzepatide (Pre). The TFEQ-R18 is a self-report questionnaire, exploring three different domains: Cognitive Restraint (CR), Uncontrolled Eating (UE) and Emotional Eating (EE) [4,30].

Adverse events (nausea, vomiting, diarrhoea, constipation) were recorded dichotomously (yes/no).

Continuous variables were tested for normality using the Shapiro–Wilk test. Given that, except for age, none of the continuous variables were normally distributed, we reported median and interquartile range (IQR) values, and pre–post comparisons were performed using the Wilcoxon signed-rank test. Moreover, we analysed the association between treatment duration (in months) and outcome measures (Δ BMI, Δ CR, Δ UE, Δ EE), using Spearman's rank correlation coefficient (ρ).

All statistical analyses were performed using R (version 4.x, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Demographic and Clinical Characteristics

25 patients diagnosed with BD were enrolled (Table 1). 12 patients (48%) were female, the mean age was 44.8 years (SD = 13.3). The baseline BMI median was 40.3 kg/m^2 [IQR: 34.6–44.2]. The patients were taking psychotropic medications: 18 patients (72%) were on mood stabilizers, 14 (56%) on selective serotonin reuptake inhibitors (SSRIs), 2 (8%) serotonin and norepinephrine reuptake inhibitors, 1 (4%) first-generation antipsychotics, 11 (44%) second-generation antipsychotics, and 5 (20%) third-generation antipsychotics.

Table 1. Demographic and treatment characteristics of the sample.

Variable	Value
N (patients)	25
Demographic data	
Age, years (mean ± SD)	44.8 ± 13.3
Female sex, n (%)	12 (48.0%)
Male sex, n (%)	13 (52.0%)
Baseline BMI, kg/m^2, median [IQR]	40.3 [34.6–44.2]
Tirzepatide Treatment	
Treatment duration, months, median [IQR]	5.0 [2.0–7.0]
Current tirzepatide dose, mg/week, median [IQR]	5.0 [5.0–7.5]
Concurrent Psychotropic Treatments	
Mood stabilizers, n (%)	18 (72.0%)
SSRIs, n (%)	14 (56.0%)
SNRIs, n (%)	2 (8.0%)
First-generation antipsychotics, n (%)	1 (4.0%)
Second-generation antipsychotics, n (%)	11 (44.0%)
Third-generation antipsychotics, n (%)	5 (20.0%)

3.2. Tirzepatide Treatment and BMI Variations

Median Tirzepatide treatment duration was 5 months [IQR: 2–7]. Regarding the dosage, the median current dose at the time of data collection was 5 mg [5–7.5]. From a median of 40.3 kg/m^2 [IQR: 34.6–44.2] registered at the moment patients started tirzepatide, BMI decreased to 37.2 kg/m^2 [IQR: 31.2–40.2]: a significant reduction has indeed been observed (Δ: −3.3 [IQR: −5.1–−1.7], V = 0.0, $p < 0.001$, r = 0.84) (Figure 1).

From the tolerability point of view, we observed nausea in 9 patients (36%), vomiting in 3 patients (12%), diarrhea in 3 patients (12%), and constipation in 4 patients (16%). However, they were all mild side effects, which presented only at the start of therapy and did not require its interruption.

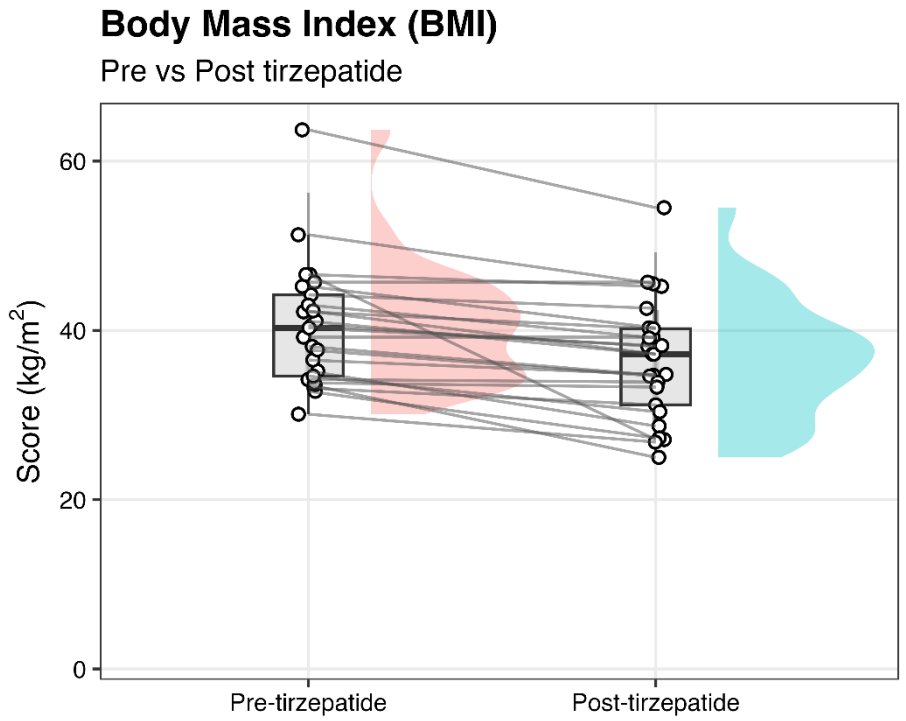

Figure 1. Body Mass Index (BMI) before and after tirzepatide treatment. Raincloud plot illustrating pre- and post-treatment BMI values (kg/m^2). Each line represents an individual patient. BMI significantly decreased following tirzepatide administration (Wilcoxon signed-rank test, $p < 0.001$).

3.3. Three-Factor Eating Questionnaire Revised-18 (TFEQ-R18)

Statistically significant improvements were observed across all TFEQ-R18 subscales (Table 2). In particular, CR scores increased significantly from pre- to post-treatment ($p < 0.001$) (Figure 2), while both UE (Figure 3) and EE (Figure 4) scores showed marked reductions (for both, $p < 0.001$).

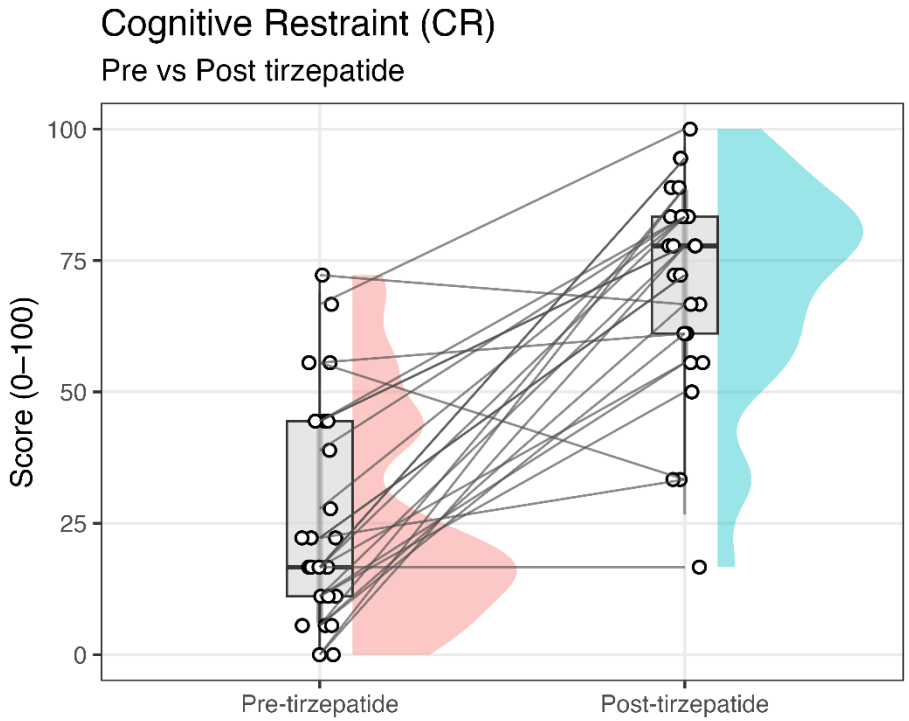

Figure 2. Cognitive Restraint (CR) scores before and after tirzepatide treatment. Raincloud plots illustrating pre- and post-treatment CR scores (0–100). Each line represents an individual patient. CR increased significantly after tirzepatide administration (Wilcoxon signed-rank test, $p < 0.001$).

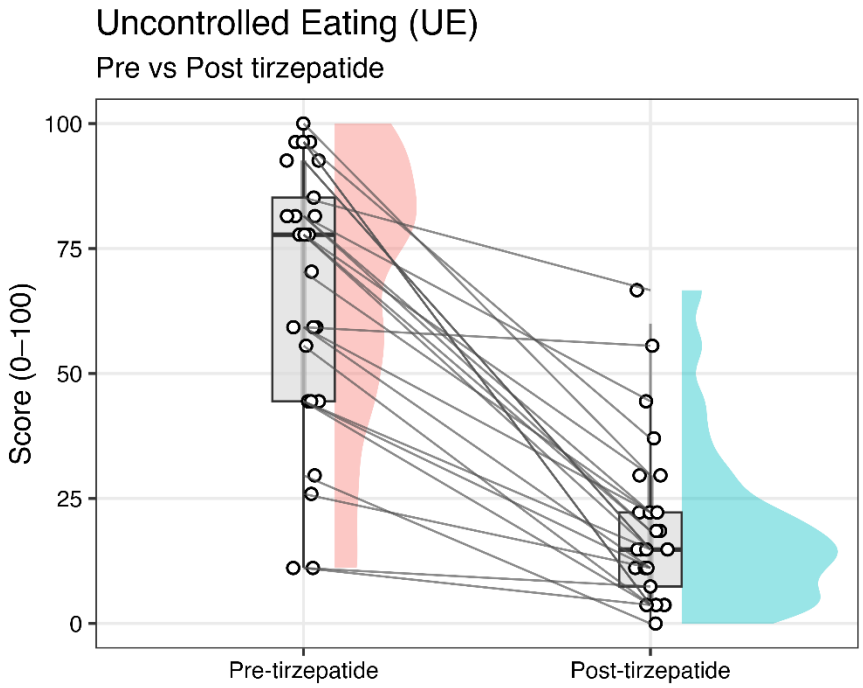

Figure 3. Uncontrolled Eating (UE) scores before and after tirzepatide treatment. Raincloud plots illustrating pre- and post-treatment UE scores (0–100). Each line represents an individual patient. UE decreased significantly after tirzepatide administration (Wilcoxon signed-rank test, $p < 0.001$).

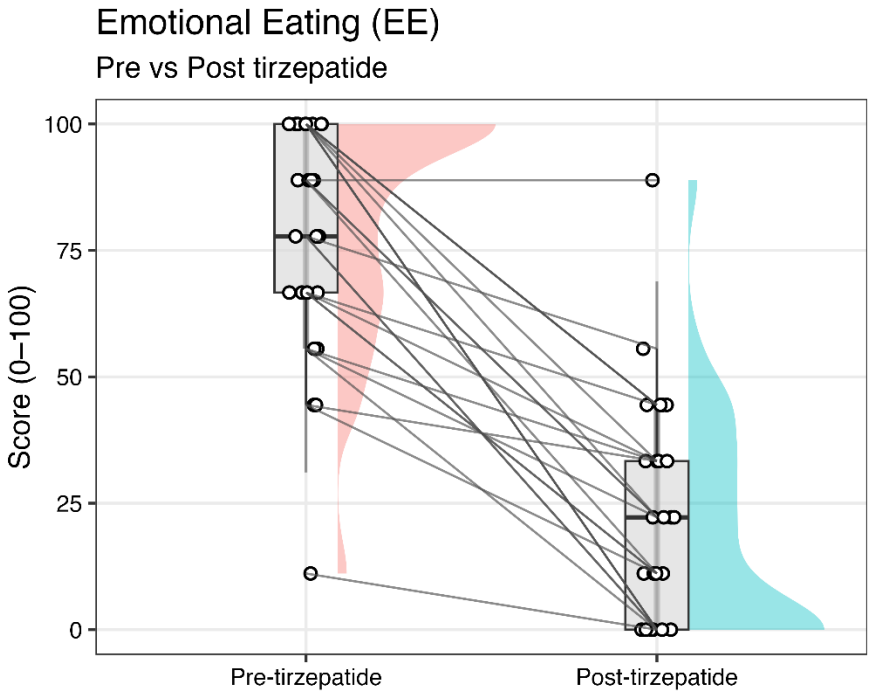

Figure 4. Emotional Eating (EE) scores before and after tirzepatide treatment. Raincloud plots illustrating pre- and post-treatment EE scores (0–100). Each line represents an individual patient. EE decreased significantly after tirzepatide administration (Wilcoxon signed-rank test, $p < 0.001$).

Table 2. Changes in TFEQ-R18 subscale scores (Pre vs. Post tirzepatide).

Subscale	Baseline (Pre)	Post-Treatment (Post)	Δ Median	95% CI (Bootstrap)	Effect Size (r)	V	*p*-Value
CR (Cognitive Restraint)	16.7 [11.1–44.4]	77.8 [61.1–83.3]	+44.4	[33.3–61.1]	0.83	5	<0.001
UE (Uncontrolled Eating)	77.8 [44.4–85.2]	14.8 [7.4–22.2]	−48.1	[−59.3–−33.3]	0.87	0	<0.001
EE (Emotional Eating)	77.8 [66.7–100.0]	22.2 [0.0–33.3]	−55.6	[−66.7–−33.3]	0.86	0	<0.001

3.4. Treatment Duration (Months) and Changes in BMI and TFEQ-R18 Subscales

Longer treatment duration was significantly associated with greater BMI reduction (Table 3) (Spearman's $\rho = -0.57$, $p = 0.003$) and with an increase in cognitive restraint ($\rho = +0.41$, $p = 0.040$). For uncontrolled eating and emotional eating, non-significant variations toward improvement were observed ($\rho = -0.19$, $p = 0.37$; $\rho = -0.08$, $p = 0.72$, respectively).

Table 3. Correlations between treatment duration and changes in BMI and TFEQ-R18 subscales (Δ = Post–Pre).

Outcome	ρ (Spearman)	*p*-Value
Δ BMI	–0.57	0.003
Δ Cognitive Restraint (CR)	+0.41	0.040
Δ Uncontrolled Eating (UE)	–0.19	0.37
Δ Emotional Eating (EE)	–0.08	0.72

4. Discussion

Obese individuals show distinctive eating-related traits: they tend to display increased food responsiveness—meaning increased sensitivity to food cues—and lower food avoidance to people with lower BMI [31]. This pattern occurs often with greater enjoyment of food, reflecting a stronger pleasure derived from eating, which has been linked to a higher risk of overeating [31]. In parallel, delay discounting is another documented feature of obesity: it consists of the tendency to favor immediate rewards, such as those provided by calorie-dense, fatty, or sugary foods, over delayed benefits [32,33]. Thus, beyond BMI reduction, obesity treatments should also address behavioral factors, which may represent underlying drivers of weight gain. This is particularly relevant in bipolar patients, who appear more vulnerable to such traits, facing an increased risk of developing obesity. Individuals with BD indeed frequently display heightened impulsivity and emotional dysregulation, even outside of acute mood episodes [34]. These traits likely extend to eating behavior, making bipolar patients more vulnerable to developing eating disorders [35]—especially those characterized by impulsive or dysregulated features, such as bulimia nervosa [18,19]. Furthermore, it has already been assessed that there is a high prevalence of emotional eating in BD [20]. Despite the evidence supporting lifestyle interventions for managing body weight in patients with BD [36], some authors have pointed out the lack of studies exploring the psychological attitudes of individuals with bipolar disorder toward food [37].

Tirzepatide, even within a relatively short timeframe, reduced the BMI of our sample in a manner consistent with the timelines reported in the literature [29], thereby demonstrating its efficacy also in patients receiving polypharmacological treatments associated with weight gain and affected by bipolar disorder, a population at higher risk. Moreover, tirzepatide has shown a good tolerability and safety profile in our cohort of bipolar patients, with only mild side effects, which did not require therapy interruption.

Our patient population benefited from tirzepatide treatment not only in terms of physical outcomes, but also in psychological dimensions related to eating attitudes and food behavior. We observed a statistically significant improvement across all TFEQ-R18 subscales, as patients demonstrated an increase in cognitive restraint toward food, becoming more capable of cognitively regulating their eating and hunger. In parallel, there was a marked reduction in both uncontrolled eating and emotional eating. This is particularly noteworthy: While the efficacy of GLP-1 receptor agonists—and tirzepatide in particular—in improving metabolic parameters and reducing weight in obesity is well established, much less is known about their psychological effects. The impact of tirzepatide on CR, UE, and EE is particularly relevant when considering how the psychopathology of bipolar disorder itself can influence these three dimensions, as already discussed. However, it should be noted that pre-treatment TFEQ-R18 scores were retrospectively rated by patients, introducing a potential recollection bias. This methodological aspect may have influenced the magnitude of the observed improvements, particularly in psychological dimensions such as emotional and uncontrolled eating.

A trial on adults with BMI from 27 to 50 kg/m^2 comparing placebo, liraglutide, and tirzepatide has already shown that tirzepatide not only reduces caloric intake but also decreases appetite, hunger, and preference for sweet/salty/fatty foods, food craving, and disinhibited eating [38]. However, that study excluded patients taking psychotropic medications known to cause weight gain. In our study, we included real-world patients who were receiving polypharmacological treatments, including mood stabilizers, antidepressants, and antipsychotics, that are known to affect body weight. Despite this, tirzepatide still proved effective in reducing BMI and in improving symptom dimensions related to eating control.

It is essential to consider the relatively short treatment duration in our study, particularly when compared to the major tirzepatide trials, which evaluated BMI changes over significantly longer periods. In line with the

literature [29,39,40], our correlation analysis revealed a greater reduction in BMI among patients treated with tirzepatide for a longer duration. Interestingly, in our sample, the CR dimension also appeared to improve over time, while UE and EE, although showing variations toward improvement with longer treatment, did not reach statistical significance. On the one hand, this suggests that patients may gradually develop better cognitive strategies to regulate their eating behavior. On the other hand, it is worth highlighting that improvements across all psychological dimensions were already evident even within a short timeframe.

While the behavioral improvements observed in our study may be primarily attributable to tirzepatide, it is important to acknowledge that concomitant treatments—particularly lithium—could have contributed to the overall effects. Lithium has been shown to modulate impulsivity and emotional dysregulation, dimensions that closely interact with eating-related psychopathology [41,42]. Although the modest weight changes associated with lithium are thought to result mainly from metabolic rather than behavioral mechanisms [42] its stabilizing effects on affect and impulse control could have partially influenced the improvements in eating behavior. Therefore, the present results should be interpreted as reflecting a potential adjunctive effect of tirzepatide within a complex pharmacological regimen.

Several hypotheses have been put forward to explain tirzepatide's effectiveness on psychic dimensions. First, tirzepatide acts on both GLP-1 and GIP receptors, which, beyond their role in the gastrointestinal system, are also expressed in the central nervous system [43]. They are particularly abundant in the nucleus tractus solitarius and the arcuate nucleus of the hypothalamus, where they appear to regulate not only energy homeostasis but also satiety and the hedonic aspects of food intake [44]. In this regard, these receptors are also found in the nucleus accumbens, the ventral tegmental area, and the prefrontal cortex [43]. Notably, GLP-1 receptor activation has been shown to recalibrate mesolimbic dopamine signaling in a context-dependent fashion—maintaining normal baseline dopaminergic tone while selectively dampening the hyperactivity induced by food- or drug-related rewards [43].

5. Limitations

This study has several limitations that should be acknowledged. First, it was not originally designed to assess the present primary outcomes; rather, the current analysis represents a post hoc, exploratory investigation derived from a broader study focused on lithium and thyroid function. The small sample size inevitably restricts the generalizability of the findings. Nonetheless, we chose to report these data given the absence of previous studies investigating tirzepatide in patients with bipolar disorder. Furthermore, the recall bias should be assessed: patients were asked to complete the TFEQ-R18 by retrospectively rating their eating behaviors before starting tirzepatide. This approach highlights the subjective improvement perceived by patients, serving as a meaningful patient-reported outcome measure (PROM). However, it also raises concerns about the accuracy of recalled pre-treatment scores. In addition, it would have been valuable to disentangle the potential influence of individual psychotropic medications on both weight changes and TFEQ-R18 subscales, but this was not feasible due to the wide variety of treatments and the small sample size. Lastly, although previous tirzepatide trials have also used relatively short follow-up periods [38], longer observational time periods would be necessary to confirm the persistence of these effects.

6. Conclusions and Future Perspectives

In this exploratory study, patients with obesity and BD were evaluated under treatment with tirzepatide, assessing not only its impact on weight reduction but also on psychological dimensions related to eating behavior. We observed significant improvements in cognitive restraint, emotional eating, and uncontrolled eating. These findings encourage larger-scale investigations of a pharmacological treatment that has already proven effective for the metabolic profile of patients with bipolar disorder but may also exert beneficial effects on psychological traits of BD that contribute to obesity risk.

Author Contributions

S.P.: conceptualization, methodology, software, data curation, writing—original draft preparation; M.P.: data curation; I.G.: data curation; M.B.R.: data curation; A.C.: supervision, validation, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study received ethical approval from the institutional review board of the Comitato Etico Regione Toscana—Area Vasta Sud Est (protocol number 26967). Prior to data collection, all participants provided written informed consent after receiving a comprehensive explanation of the study's objectives and procedures. The research was conducted in full compliance with the principles outlined in the Declaration of Helsinki and adhered to Good Clinical Practice (GCP) guidelines.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data supporting this study may be available from the corresponding author upon reasonable request.

Conflicts of Interest

Alessandro Cuomo has been a consultant and/or speaker for Angelini, GlaxoSmithKline, Lundbeck, Janssen, Otsuka, Pfizer, and Recordati. He reports no financial relationships with Eli Lilly and Company nor with Novo Nordisk. The other authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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