Liraglutide 3.0 mg and Mental Health: Can Psychiatric Symptoms Predict Adherence to Therapy? Insights from a clinical audit

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Abstract

Introduction. The glucagon-like peptide-1 analogue liraglutide 3.0 mg is an out-of-pocket medication approved for weight management in obesity. We aimed to investigate the relationship between psychiatric symptoms (i.e., depression, anxiety, binge eating) and adherence to therapy.

Methods. A clinical audit was carried out on 54 adults with obesity treated with liraglutide 3.0 mg. We retrospectively analyzed the relation between (1) psychiatric symptoms evaluated through the State-Trait Anxiety Inventory (STAI-Y1), the Beck Depression Inventory (BDI), the Binge Eating Scale (BES); and (2) adherence to therapy by assessing the maximum dosage (MD) and treatment duration (TD).

Results. In the whole cohort, the average weight loss was 4.43% (± SD = 5.5). We found a negative correlation between anxiety symptoms (STAI-Y1 score) and MD (r=-.276), between depression symptoms (BDI score) and TD (r=-.276), and between a high probability of binge eating (BES score > 17) and TD (r=-.275). Linear regression analysis demonstrated that STAI-Y1 score predicted MD \([R^2 = .076, p = .044]\), BDI score predicted TD \([R^2 = .076, p = .044]\), and significant binge eating predicted TD \([R^2 = .076, p = .044]\). Despite the lower adherence, the presence of psychiatric symptoms did not lead to a reduction in drug effectiveness on weight loss.

Conclusion. Psychiatric symptoms can predict reduced adherence to liraglutide 3.0 mg therapy in real life. However, this does not appear to jeopardize its effect on weight loss. These findings suggest that persons with obesity and impaired mental health can also benefit from treatment.

Level of evidence. Level V, descriptive studies.

What Is Already Known On This Subject?

The glucagon-like peptide-1 analogue liraglutide has been shown to be effective in improving both metabolic profile and mental health. Factors affecting adherence to therapy are still poorly understood: it is necessary to investigate the role of psychiatric symptoms.

What does this study add?

This study highlights that psychiatric symptoms such as greater anxiety symptoms, greater depressive symptoms, and significant binge eating can predict a reduced adherence to liraglutide 3.0 therapy. However, despite the lower adherence, the presence of psychiatric symptoms did not lead to a reduction in drug effectiveness on weight loss. Patients with psychiatric symptoms can benefit from treatment. However, appropriate efforts should be made to overcome barriers and increase adherence in the National Health Service outpatient obesity clinic setting.

1. Introduction
The World Health Organization has defined adherence as "the extent to which a person's behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [1]. Adherence has been found to be related to patient characteristics as well as aspects regarding disease and treatment [1]. Obesity is now regarded as a chronic, progressive, and relapsing disease [2, 3]. Several studies show that obesity treatment is hampered by poor attendance and adherence rates [4, 5]. The recent availability of novel pharmacological treatments for this disease, suitable for long-term use, stresses the need to investigate factors related to adherence in persons living with obesity.

The glucagon-like peptide-1 receptor agonists (GLP-1 RAs) work by activating the GLP-1R receptors. They are effective in reducing energy intake both peripherally, increasing stimulation of insulin secretion, and centrally, promoting satiety through their hypothalamic action [6, 7]. They were first introduced in 2005 for treating type 2 diabetes (T2DM), an area in which they have demonstrated remarkable efficacy and safety [8–10]. GLP-1 RAs have common mechanisms of action: augmentation of glucose-insulin secretion, suppression of glucagon secretion, delayed gastric emptying, attenuation of the release of hypothalamic orexigenic neuropeptides, and promotion of the release of anorexigenic neuropeptides [11, 12]. The sum of these effects leads to a reduction in weight, body mass index (BMI), glycated hemoglobin A1c, and systolic blood pressure [11, 13].

In light of their broad efficacy, GLP-1 RAs have more recently been considered for treating obesity also in the absence of T2DM [14–16]. Liraglutide 3.0 mg, the first GLP-1 RA used in the treatment of obesity, was approved in 2014 by Food and Drug Administration (FDA) and in 2015 by European Medicines Agency (EMA) [17]. It has proved to be an effective tool, in adjunct to a hypocaloric diet and physical activity program, for achieving clinically relevant weight loss (≥5%) in adults with excess weight (BMI ≥ 27) who also have weight-related medical problems or obesity (BMI ≥ 30) [14, 18]. It shows overall good tolerance despite the common side effects related to the gastrointestinal system, primarily nausea, usually of mild or moderate severity [18, 19].

In addition to their metabolic effect, GLP-1 RAs have also shown relevant effects in mental health. In particular, an increasing amount of research focuses on GLP-1 RAs efficacy in reducing anxiety and depressive symptoms, highlighting an important connection between metabolic regulations and psychopathological mechanisms [20–24]. In fact, recent studies point out that disturbed homeostasis between the nervous system and the immune and endocrine systems, disturbances in cerebral energy metabolism, and dysfunction of the gut-brain axis could play an important role in the pathogenesis of depression and anxiety: GLP-1RAs, through a modulatory effect on the immune, endocrine, and metabolic processes in the central nervous system, appear to act actively in ameliorating these symptoms [20, 25].

While these results begin to shed light on liraglutide's impact on mental health, on the other hand, to our knowledge, it has not been demonstrated how mental health may conversely have an impact on long-term therapies such as those with GLP-1RAs. Therefore, we carried out a clinical audit aimed at exploring the relationship between psychiatric symptoms – i.e., depression, anxiety, and binge eating – and both
adherence and effectiveness of liraglutide 3.0 mg therapy in our cohort of patients followed in a National Health Service outpatient obesity clinic.

2. Methods

2.1. Study Design and Participants

A clinical audit was carried out by retrospectively collecting data from outpatients' electronic medical records at our Unit of Clinical Nutrition and Metabolism of Sant'Orsola-Malpighi Hospital in Bologna, Italy. The procedures of this report are part of our clinical practice, and patients had provided their consent to data collection before receiving clinical services, in addition to the standard obligation for privacy. The audit of collected data and their statistical evaluation was carried out after complete anonymization. As standard practice, we ask all patients to complete and return a battery of self-administered psychometric tests (see below).

We screened all adult outpatients, consecutively referring to the Unit of Clinical Nutrition and Metabolism from June 2019 to November 2022. Patients initiating treatment with liraglutide 3.0 mg were eligible for inclusion if they had: (a) a body mass index (BMI) $\geq 30$ kg/m$^2$ or a BMI of $\geq 27$ mg/m$^2$ with at least one treated weight-related comorbidity (b) age $\geq 18$ years old at the time of assessment; (c) completed the psychometric assessment; (d) received liraglutide 3.0 mg prescription by August 2022 and had at least two months of follow-up. The exclusion criterion was taking liraglutide without following the recommended dosing escalation schedule as described in the drug datasheet and/or as prescribed by the clinician.

It is important to underline that the management of patients followed by our center follows a specific procedure. All patients first seen inside the center are invited to participate in structured behavioral programs modulated according to the severity of their weight excess and unhealthy eating pattern. At any follow-up visit, patients receive motivational reinforcement on lifestyle changes and adherence to a healthy diet and habitual physical activity. Drug therapy is considered if the first line of behavioral treatment failed to meet the expected minimum target (i.e., weight loss of at least 3% in three months) or if there is a significant history of previous unsuccessful weight loss attempts.

According to the prescribing information for Liraglutide 3.0 mg, the starting dose of 0.6 mg per day should be increased in weekly increments over four weeks to a recommended maintenance dose of 3.0 mg from the fifth week onward. Treatment should be discontinued after 12 weeks if the patient has not attained a weight reduction $\geq 5\%$ of the starting weight [17] (Saxenda®; Novo Nordisk A/S, Copenhagen, Denmark). For this purpose, we considered the starting weight the one at the initial visit to the Centre.

During the Covid-19 pandemic, most follow-up visits were conducted remotely (via video and phone calls). Therefore, measured patients’ weight was not available for all patients at 12 weeks but was instead measured at the next examination carried out in presence.
2.2. Procedures and Measures

For the purposes of this study, variables collected by clinicians as part of standard consultation and follow-up visits were used. The information was collected through electronic medical records (EMRs) and included socio-demographic data, recent and past medical history, current medications, the timing of follow-up visits, the dosage of liraglutide at the time of the visit, and side effects reported from visit to visit.

All patients filled in the Italian version of the State-Trait Anxiety Inventory (STAI-Y1) [26], Beck Depression Inventory [27] (BDI), and Binge Eating Scale (BES) [28]. STAI-Y1 is a 20-item self-report assessing trait anxiety; BDI is a 21-item self-report measuring characteristic attitudes and symptoms of depression; and BES is a 16-item self-report questionnaire designed to capture the behavioral, cognitive, and emotional features of objective binge eating in adults with obesity and overweight; BES scores above 17 are considered suggestive of significant binge eating (BE) [29].

To quantify adherence to liraglutide therapy, we collected data on treatment duration (TD), and the maximum dosage (MD) achieved.

To quantify the effectiveness of liraglutide therapy on weight loss, we collected data on weight at 12 weeks (or a closer follow-up examination). Therefore, the weight loss evaluation did not include patients with shorter follow-ups.

2.3. Statistical Analysis

Data analysis was performed using Statistical Package for Social Science for MacOS (SPSS) software, Version 27.0 (IBM Corp, Armonk, NY). Descriptive analyses were conducted by analyzing categorical variables’ frequencies (n) and percentages (%). Bivariate Pearson’s correlations were used to investigate potential relationships between STAI-Y1, BDI, and BES scores, BE expressed dichotomously, and adherence indicators (MD and TD). Linear regression analyses were performed to investigate the associations between STAI-Y1 scores and MD, BDI scores and TD, and BE and TD. Student’s T-test and one-way ANOVA were used to test differences in % weight loss at 12 weeks in dichotomous analysis (no/yes) for psychiatric symptoms and psychoactive therapy; and among subgroups graded by severity of psychiatric symptoms, respectively. All the analyses were two-sided with $\alpha = 0.05$.

3. Results

3.1. Socio-demographic results

Key socio-demographic characteristics are summarized in Table 1. Of 130 obese adults on liraglutide therapy, 66 were excluded for not having completed the psychometric assessment, four were excluded for taking liraglutide without following the recommended dosing escalation schedule as described in the drug datasheet and/or as prescribed by the clinician, and six were excluded since they had a follow-up
shorter than two months. The final sample included 54 subjects, of which the majority (n = 36; 66.7%) were female. The mean age was 48.56 (± SD = 13) years, ranging from 19 to 73 years. The mean Body Mass Index (BMI) was 39.89 (± 6.05 SD) kg/m2, ranging from 27.2 kg/m2 to 59.5 kg/m2. The average weight loss in the overall sample (n = 54) was 4.43% (± 5.5 SD); it attained 4.67% (± 5.28 SD) in the female population and 3.95% (± 6.05 SD) in the male population.

### Table 1
Socio-demographic data in the sample (N = 54)

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>36</td>
</tr>
<tr>
<td>Male gender</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean value</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19</td>
<td>73</td>
<td>48.56</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.15</td>
<td>59.49</td>
<td>39.89</td>
</tr>
</tbody>
</table>

*Legend. BMI = Body Mass Index*

Regarding the discontinuation of the drug, 32 out of 54 patients suspended the drug during the observation period (59.26% of the sample). Of these, two (6.25%) discontinued due to achievement of weight loss goal, 12 due to incomplete efficacy (37.5%), nine due to gastrointestinal side effects such as nausea, emesis, gastralgia (28.13%), and eight patients dropped out (25%). It should be specified that, of the 12 patients who discontinued for incomplete efficacy, only 5 (41.7% of them) had reached the maximum dosage of 3 mg.

Four patients did not start the prescribed treatment and dropped out after the prescription, nineteen patients had a follow-up on treatment shorter than four months, and three patients did not have a follow-up in a congruent time frame (around 12 weeks).

Consequently, only twenty-eight patients were available for evaluation of treatment effectiveness at 12 weeks (i.e. the schedule indicated in the European Medicine Agency drug prescription sheet). An average weight loss of 6.2% (± 7.6 SD) was obtained for this subcohort. Specifically, there was a decrease of 5.8% (± 7.8 SD) in females and a decrease of 7.2% (± 7.5 SD) in males.

### 3.2. Psychiatric symptoms and psychoactive treatments

Key results are summarized in Table 2. Regarding anxiety, we found mean STAI-Y1 values of 44.48 (± SD = 9.18), indicative of mild anxiety. Looking at the distribution, we identified that 35% (n = 19) of subjects did not suffer from clinically significant anxiety (STAI-Y1 score < 40), 31% (n = 20) of subjects suffered from mild anxiety (STAI-Y1 score 40–49), 24% (n = 13) of subjects suffered from moderate anxiety (STAI-Y1 score 50–59), and 3.7% (n = 2) suffered from severe anxiety (STAI-Y1 ≥ 60).
Table 2

<table>
<thead>
<tr>
<th>Psychometric scales, graded by severity (number of subjects; percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below threshold</td>
</tr>
<tr>
<td>STAI-Y1 &lt; 40</td>
</tr>
<tr>
<td>STAI-Y1 19; 35.2%</td>
</tr>
<tr>
<td>BDI &lt; 10</td>
</tr>
<tr>
<td>BDI 17; 31.5%</td>
</tr>
<tr>
<td>BES &lt; 17</td>
</tr>
<tr>
<td>BES 35; 65%</td>
</tr>
</tbody>
</table>

Legend. SD = standard deviation; STAI-Y1 = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; BES = Binge Eating Scale

Concerning depression, we found mean BDI values of 13.54 (± SD = 8.12), indicative of mild depression. Looking at the distribution, we identified that 31% (n = 17) of subjects did not suffer from clinically significant depression (BDI score < 10), 46% (n = 25) of subjects suffered from mild depression (BDI score 10–19), 19% (n = 10) of subjects suffered from moderate depression (BDI score 20–29), and 3.7% (n = 2) suffered from severe depression (BDI score ≥ 30).

Regarding binge eating, we identified mean BES values of 15.46 (± SD = 9.59), indicative of no significant BE. Indeed, 65% (n = 35) of the sample had no significant BE (BES score < 17). The remaining 35% (n = 29) had significant BE (BES score > 17): 18.5% (n = 10) of the sample had moderate levels of BE (BES score 17–26), and 17.5% (n = 9) had severe levels of BE (BES score ≥ 26).

Twelve patients were on single-drug antidepressant and/or antianxiety and/or antipsychotic treatment (3 vortioxetine, 3 escitalopram, 2 sertraline, 1 paroxetine, 1 duloxetine, 1 aripiprazole, 1 etizolam); four patients were on combination psychotropic treatment (1 sodium valproate + sertraline + trazodone; 1 olanzapine + trazodone + pregabalin; 1 venlafaxine + trazodone + pregabalin, 1 olanzapine + fluoxetine). In another two patients, antidepressant therapy (one venlafaxine, one fluoxetine) was started at the same time as Liraglutide 3.0. Overall, one-third of patients resulted in psychotropic treatment during Liraglutide therapy.

### 3.3. Adherence indicators

MD had a range between 0.6 mg and 3 mg, with a mean value of 2.1 mg (± SD = 0.71). TD had a mean value of 177.2 days, with a minimum of 0 days and a maximum of 632 days. Adherence indicators results among subgroups graded by severity of psychiatric symptoms are summarized in Table 3.
Table 3
Psychometric scales and adherence indicators

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean value</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI-Y1 score</td>
<td>28</td>
<td>68</td>
<td>44.48</td>
<td>9.18</td>
</tr>
<tr>
<td>BDI score</td>
<td>0</td>
<td>37</td>
<td>13.54</td>
<td>8.12</td>
</tr>
<tr>
<td>BES score</td>
<td>0</td>
<td>35</td>
<td>15.46</td>
<td>9.59</td>
</tr>
<tr>
<td>MD (mg)</td>
<td>0.6</td>
<td>3</td>
<td>2.1</td>
<td>0.71</td>
</tr>
<tr>
<td>TD (days)</td>
<td>0</td>
<td>632</td>
<td>177.2</td>
<td>155.2</td>
</tr>
</tbody>
</table>

Legend. SD = standard deviation; STAI-Y1 = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; BES = Binge Eating Scale; MD = maximum dosage; TD = treatment duration

Table 4
Percentage of weight loss at 12 weeks according subcategories of psychiatric symptoms (in brackets absolute number of subjects)

<table>
<thead>
<tr>
<th></th>
<th>Below threshold</th>
<th>Mild</th>
<th>Moderate to Severe</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI-Y1 &lt; 40</td>
<td>(n = 12)</td>
<td>STAI-Y1 40–49 (n = 10)</td>
<td>STAI-Y1 ≥ 50 (n = 6)</td>
<td></td>
</tr>
<tr>
<td>% WL (± SD)</td>
<td>8.8 ± 6.1</td>
<td>6.6 ± 10.6</td>
<td>3.0 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>BDI &lt; 10</td>
<td>(n = 10)</td>
<td>BDI 10–19 (n = 14)</td>
<td>BDI 20–29 (n = 4)</td>
<td></td>
</tr>
<tr>
<td>% WL (± SD)</td>
<td>9.1 ± 6.2</td>
<td>5.2 ± 8.1</td>
<td>5.7 ± 8.7</td>
<td>NS</td>
</tr>
<tr>
<td>BES &lt; 17</td>
<td>(n = 22)</td>
<td>BES 17–26 (n = 4)</td>
<td>BES &gt; 27 (n = 4)</td>
<td></td>
</tr>
<tr>
<td>% WL (± SD)</td>
<td>7.1 ± 7.9</td>
<td>8.1 ± 6.0</td>
<td>-0.8 ± 3.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Legend. SD = standard deviation; STAI-Y1 = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; BES = Binge Eating Scale; % WL = Percentage of Weight Loss; SD = Standard Deviation

3.4. Associations between psychiatric symptoms and adherence indicators

Bivariate correlation analyses demonstrated a negative correlation between STAI-Y1 and MD (r = −.276) and a negative correlation between BDI and TD (r = −.276) (Fig. 1). Since no significant correlation emerged between BES and adherence indicators, we created the categorical variable binge eating (BE) based on its BES cut-off (BES > 17): we found a negative correlation between a significant BE and TD (r = −.275) (Fig. 1).
Linear regression analyses demonstrated that STAI-Y1 significantly predicted MD \([F(1, 53) = 4.279, R^2 = .076, \text{Unstandardized } B = -.021, p = .044]\), that BDI significantly predicted TD \([F(1, 53) = 4.280, R^2 = .076, \text{Unstandardized } B = -.5.271, p = .044]\), and that a significant BE significantly predicted TD \([F(1, 53) = 4.258, R^2 = .076, \text{Unstandardized } B = -88.582, p = .044]\) (Figs. 2–4).

These results highlight that greater anxiety symptoms can predict a lower MD; greater depressive symptoms and a significant BE can predict a shorter TD.

Both MD and TD did not significantly differ between those who were and those who were not on psychotropic treatment.

### 3.5. Relationship between psychiatric symptoms and weight loss

We observed no correlations between psychometric scores and percent weight loss in the overall sample \((n = 54)\). However, there was a trend close to statistical significance \((p = 0.053, \text{Mann Whitney U test})\) for lower weight loss in those being on psychoactive medications.

We evaluated the relationship between the severity of psychiatric symptoms and % weight loss in the subsample of patients \((n = 28)\) available for evaluation of treatment effectiveness at 12 weeks. The weight loss according to subcategories of psychiatric symptoms is shown in Table 2. No difference was found in % weight loss across subgroups graded by severity of anxiety and depression. However, there was a non-significant trend \((p = 0.132)\) for differences in % weight loss according to BES subcategories. Linear regression analysis demonstrated that BES significantly predicted the percentage of weight loss in the subsample at 12 weeks \([F(1, 26) = 7.495, R^2 = .231, \text{Unstandardized } B = -.3.270, p = .011]\). However, this statistical significance was not confirmed when we considered the total effect on weight in the overall sample \((n = 54)\) and during the whole observation period. We again observed a non-significant trend \((p = 0.07)\) towards a lower % weight loss at 12 weeks in those who were on psychotropic treatment as compared with those who were not.

No significant differences in % weight loss - either in the subsample at 12 weeks and in the overall sample - were found by dichotomizing groups in terms of the presence/absence of psychiatric symptoms.

### 4. Discussion

To our knowledge, this is the first real-world study investigating the relationship between psychiatric symptoms and adherence to liraglutide 3.0 as obesity therapy. We found an inverse correlation between adherence indicators and the presence and intensity of anxiety, depression, and eating compulsivity, as detected by psychometric tests. Through regression analysis, we showed that greater anxiety symptomatology might predict a lower MD; greater depressive symptomatology and significant BE may predict a shorter TD. Nevertheless, we were able to observe that, despite the effect on adherence, neither
the presence of psychiatric symptoms nor being on psychoactive therapies led to a significant reduction in overall liraglutide effectiveness on weight loss.

Our results align with previous literature on poor adherence to therapy by obese patients presenting anxiety-depressive symptomatology [30]. It is generally known that depression and anxiety are associated with lower compliance and adherence to medication [31–34]. Moreover, it has been shown that antidepressants can diminish the weight loss effect of GLP-1 RAs, which could decrease compliance with therapy [35]. Overall, because the association between obesity, anxiety-depressive syndrome, and antidepressant therapy occurs frequently, patients often face multiple conditions that feed off each other clinically and in terms of treatment adherence [36].

In the present audit, being on psychotropic (mainly antidepressant) therapy did not affect adherence, although we observed in this subgroup a non-significant trend for lower weight loss (at 12 weeks and overall).

Regarding specific adherence to liraglutide, intrinsic aspects related to the drug should be considered. First, side effects such as nausea, constipation, diarrhea, and vomiting, usually mild and transient, might be differently tolerated in more anxious people [37, 18]. Second, we must consider that out-of-pocket medications (as in the case of liraglutide 3.0 mg for Italian patients) have been shown to have a negative impact on adherence [38, 39].

The uniqueness of this work lies in the fact that we identified a predictive effect of psychiatric symptoms on adherence to liraglutide therapy, a drug that has peculiarly demonstrated efficacy on both metabolic and psychiatric symptoms: we can now hypothesize that promoting greater compliance in our patients could foster a virtuous circle in which physical and mental health have a mutually beneficial effect. Indeed, research has demonstrated a bidirectional relationship between obesity and depression [40, 41], inflammation and depression [42, 43], obesity and inflammation [44, 45], and inflammation and anxiety [46]. Research has shown that anxious-depressive states and obesity are associated with similar changes in central nervous system cells due to the exaggerated action of glucocorticoids, proinflammatory cytokines, or glutamate [40, 20, 21]. In particular, an excess of glucocorticoids can lead to impaired insulin action and glucose metabolism, limited energy intake for proper neuronal functioning, and, consequently, disturbed synaptic plasticity [40, 20, 21].

Due to this complex link between metabolic, inflammatory, and psychic balance, therapies that reduce blood glucose levels, improve central inflammation, and regulate the hypothalamic-pituitary-adrenal axis have been shown to reduce depressive symptoms [25]. This mechanism is effective in traditional anti-hyperglycemic agents, such as insulin or metformin, and the newer GLP-1 RAs [21]. Indeed, research has amply demonstrated that the use of GLP-1 RAs in T2DM patients is associated with a lower incidence of depression and anxiety compared to controls treated with different therapies [47, 48, 23]. In addition, recent studies evaluating the gut microbiota have suggested that one of the roles of GLP-1 RAs in treating anxiety is related to improved glucoregulation, leading to reduced proinflammatory cytokines and increased neuroprotection [49]. It is worth mentioning that in the obesity treatment toolkit the drug
naltrexone/bupropion is also available: this is a fixed-dose synergistic combination of two molecules originally used to treat opioid/alcohol use disorders and depression [50]. It is effective in reducing appetite and increasing energy expenditure, helping to stick to a calorie-controlled diet and to reduce body weight: according to Canadian guidelines, it is the first drug of choice for BMI $\geq 30$ kg/m$^2$ or BMI $\geq 27$ kg/m$^2$ plus obesity-related comorbidities who present symptoms such as craving or depression [51].

Thus, there are numerous reasons not only to counteract clinical inertia by offering pharmacological treatment for obesity to patients with psychiatric symptoms but also to direct therapy toward pathophysiological pathways shared between physical and mental health: taking care of one means taking care of the other as well.

4.1. Strength and limits

Strengths of this study include the real-life setting in a public outpatient obesity clinic, therefore less prone to selection bias than randomized controlled trials – which tend to select those patients with higher adherence [52, 53]. This setting was also more representative of the problems clinicians can face while prescribing a drug that is not covered by the National Health Service – unlike most medications for clinically relevant diseases. Furthermore, this study is based on the routine collection of psychiatric symptoms in the context of the first visit to the Unit of Clinical Nutrition and Metabolism, performing in the internal medicine setting, a type of assessment that is generally reserved for the psychiatric setting.

These findings should also be considered in light of the limitations that this clinical audit presents: (1) we observed subjects retrospectively; (2) the sample size was relatively small; only half of the sample had, in fact, completed/returned the psychodiagnostic scales, the main reason being the logistical difficulties related to Covid-19 pandemic; (3) it was only sometimes possible to precisely trace why the treatment was discontinued, denying the possibility of more specific statistical analyses on the issue of side effects.

4.2. Conclusions

In conclusion, we can observe a close relationship between psychiatric symptoms – i.e., depression, anxiety, and binge eating – and reduced adherence to liraglutide therapy. Deepening this knowledge could allow us to identify targeted treatments for our patients. An integrated approach to managing these individuals could ensure a reduction in psychiatric symptoms and greater therapeutic adherence, ultimately leading to better overall health.

Declarations

Funding

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Competing Interests

MLP has received honoraria for lectures from Novo Nordisk and Bruno Farmaceutici, for advisory boards from Novo Nordisk and has participated in sponsored studies by Novo Nordisk. The remaining authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Conceptualization, MLP and STV; methodology, MLP and STV; formal analysis, MLP and STV; data curation, STV and MS; writing-original draft preparation, STV, MS and MLP, writing-review and editing, MLP; supervision, MLP and LP. All authors have read and agreed to the published version of the manuscript.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The procedures of this report are part of our clinical practice. The audit of collected data and their statistical evaluation was carried out after complete anonymization.

Consent to participate

Patients had provided their consent to data collection prior to receiving clinical services, in addition to the standard obligation for privacy.

References


Figures

<table>
<thead>
<tr>
<th>STAI-Y1</th>
<th>BDI</th>
<th>BE</th>
<th>MD</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI-Y1</td>
<td>-</td>
<td>.459**</td>
<td>.238</td>
<td>-.276*</td>
</tr>
<tr>
<td>BDI</td>
<td>.459**</td>
<td>-</td>
<td>.317*</td>
<td>-.025</td>
</tr>
<tr>
<td>BE</td>
<td>.238</td>
<td>.317*</td>
<td>-</td>
<td>-.050</td>
</tr>
<tr>
<td>MD</td>
<td>-.276*</td>
<td>-.025</td>
<td>-.050</td>
<td>-</td>
</tr>
<tr>
<td>TD</td>
<td>-.224</td>
<td>-.276*</td>
<td>-.275*</td>
<td>.341*</td>
</tr>
</tbody>
</table>

Legend: SD = standard deviation; STAI-Y1 = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; BE = significant binge eating; MD = maximum dosage; TD = treatment duration; * = significant correlation; ** = strong significant correlation

Figure 1
Pearson's Correlations Heatmap. Higher correlations are marked with darker shades, lower correlations with lighter shades.

Figure 2

Linear Regression Model between STAI-Y1 (independent variable/predictor) and MD (dependent variable)

Legend. MD = Maximum Dosage; STAI-Y1 = State-Trait Anxiety Inventory
Figure 3

Linear Regression Model between BDI (independent variable/predictor) and TD (dependent variable)

Legend. TD = Treatment Duration; BDI = Beck Depression Inventory
Figure 4

Linear Regression Model between BE (independent variable/predictor) and TD (dependent variable)

Legend. TD = Treatment Duration; BE = Significant Binge Eating