Postoperative continuation of antidepressant therapy is associated with reduced short-term weight loss following Roux-en-Y gastric bypass surgery

Manuscript

Title

Postoperative continuation of antidepressant therapy is associated with short-term reduced weight loss following Roux-en-Y Gastric Bypass surgery: a retrospective cohort study.

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Abstract

Purpose: Bariatric surgery candidates are frequently treated with antidepressants. Several of these drugs have~~n~~ been associated with weight gain and ~~could~~ potentially interfere with ~~the~~ weight loss after bariatric surgery. This retrospective cohort study aimed to investigate the short-term- effects of antidepressants on ~~the~~ weight loss during the first 24 months after a Roux-en-Y Gastric Bypass.

Methods: Patients with a fully documented antidepressant ~~therapy~~ treatment status for at least 12 months were included. Weight loss was expressed as the % excess BMI loss (%EBMIL) or % total weight loss (%TWL). A mixed linear effects model was used to determine the impact of continued and discontinued ~~therapy~~ treatment with antidepressants on weight loss.

Results: A total of 751 patients were included in this study. At 24 months, patients had lost 77.38 ±30.10 %EBMIL (30.63 ±13.12 %TWL). In patients treated with antidepressants (n=125) the %EBMIL and %TWL was reduced with -2.81% (p=0.025) and -1.36% (p=0.002) respectively, and with -5.52 %EBMIL (p<0.001; -1.05 %TWL, p=0.012) after multivariate adjustment. Serotonin-norepinephrine reuptake inhibitors (-12.47 %EBMIL, p<0.001) and tricyclic antidepressants (-11.01 %EBMIL, p=0.042) were predominantly responsible for worse outcomes. Beyond 24 months, at 36 months (-4.83%, p<0.001) and 48 months (-3.54%, p=0.006), the %EBMIL was still reduced. In contrast, early postoperative discontinuation of antidepressants did not influence two-year outcomes.

Conclusions: Treatment with antidepressants was associated with reduced weight loss after gastric bypass surgery, but only if treatment was continued for at least one year postoperatively. Mainly tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors were responsible for this reduction in weight loss.

Keywords: Gastric Bypass, Antidepressants, Weight Loss, Surgery Outcomes, Bariatric Surgery

Authors' Contributions

- Plaeke P: Study Conception and Design, Acquisition of Data, Analysis and Interpretation of Data, Drafting of Manuscript, Critical Revision of Manuscript

- Van Den Eede F: Analysis and Interpretation of Data, Drafting of Manuscript, Critical Revision of Manuscript

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Abbreviations

RYGB - Roux-en-Y Gastric Bypass
BMI - Body Mass Index (Weight/Length^2)
%EBMIL - Percentage Excess BMI Loss
%TWL - Percentage Total Weight Loss
SSRI - Selective Serotonin Reuptake Inhibitor
SNRI - Serotonin ~~and~~ Norepinephrine Reuptake Inhibitor
TCA - Tricyclic Antidepressant
NDRI - Norepinephrine and Dopamine Reuptake Inhibitor
95%CI - 95% Confidence Interval
SD - Standard Deviation
HDL - High-Density-Lipoprotein
Suppl. Table - Supplementary Table

Formulas

$$\%\text{EBMIL} = \frac{(\text{Preoperative BMI} - \text{BMI at timepoint})}{(\text{Preoperative BMI} - 25\ \text{kg/m}^2)} \times 100$$

$$\%\text{TWL} = \frac{(\text{Preoperative Weight} - \text{Weight at timepoint})}{\text{Preoperative weight}} \times 100$$

Introduction

Bariatric surgery has been proven to be one of the most effective interventions to achieve weight loss in morbidly obese patients and as a result, bariatric procedures are among the most commonly performed procedures in developed countries. In general, following a Roux-en-Y Gastric Bypass (RYGB) patients on average lose 60-75% of their excess body weight [1,2]. The importance of this weight loss is reflected in the positive effects of bariatric surgery on several comorbidities, including arterial hypertension, type II diabetes mellitus, obstructive sleep apnea syndrome and liver steatosis.

Yet, while considerable weight loss is achieved in almost every patient, the extent of the final weight loss achieved up to two years after surgery seems to vary from patient to patient. Although physical, metabolic and dietary factors definitely seem to play a role in these variations in outcome, psychological factors have also been reported to be responsible [3-6]. It has been established that psychiatric disorders tend to be more common in patients with obesity. In addition, patients with obesity and a concurrent psychiatric burden also more often seek surgical intervention for their obesity [7,8]. In a recent meta-analysis, the prevalence of mood disorders among bariatric surgery candidates was estimated at 23%, more than double of the 10% estimated prevalence in the general US population [8].

As a result, many patients are treated with psychotropic drugs, including antidepressants, at the time of the bariatric procedure [9]. Several of these drugs have been associated with undesired changes in body weight, and significant drug-induced weight gain is a common reason why patients discontinue or modify their treatment [10,11]. As several classes of antidepressants have the potential to interact with different metabolic pathways through a wide array of mechanisms, these drugs could potentially also interfere with the weight loss following bariatric surgery.

Therefore, the primary outcome of this study was to investigate the general effect of antidepressants on weight loss up to 24 months after RYGB surgery. Secondary aims included measuring the effects of major types of antidepressants, investigating the influence of antidepressant discontinuation on weight loss induced by the RYGB, and determining whether these effects persisted beyond two years after the surgical intervention.

Materials and Methods

Study population

Out of all patients who underwent bariatric surgery in the Antwerp University Hospital between January 2008 and January 2018, patients undergoing a RYGB procedure were selected for inclusion in this retrospective cohort study. Data of these patients had to strictly comply with preset inclusion and exclusion criteria. As this study aimed to determine the effects of continuous antidepressant therapy during the first 12 months after a RYGB, full electronic patients records containing the medical treatment and therapy with antidepressants at the time of the

procedure and one year later were required. The patients' mental health status was routinely assessed in preoperative semi-structured interviews conducted at our hospital's psychiatry department.

Weight loss after bariatric surgery normally stabilizes within 12 to 24 months after bariatric surgery. Therefore only patients with at least 12 months of follow-up, and with documented stabilization of their body weight within the first 24 months after surgery were included in the primary analysis. Finally, a body mass index (BMI) of at least 40.0 kg/m² or 35.0 kg/m² with type 2 diabetes mellitus, obstructive sleep apnea or therapy-resistant arterial hypertension was required to qualify for surgery. Patients with incomplete follow-up, with an unknown antidepressant therapy status or who underwent a bariatric procedure other than the RYGB, were excluded. Conversions from a failed gastric banding or Mason gastroplasty to a RYGB were not excluded.

Outcome measures

Weight loss was measured as the percentage excess BMI loss (%EBMIL), with a BMI of 25.0 kg/m² as the ideal weight equivalent, and the total weight loss (%TWL). For every patient the use of antidepressants at the time of surgery and one year later were registered. Antidepressants were divided into 5 classes based upon their mechanism of action: selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), trazodone, and norepinephrine-dopamine reuptake inhibitors (NDRI). Monoamine oxidase inhibitors, st. John's Wort, mirtazapine, and mood stabilizers like lithium were not taken into consideration in this study.

In addition, data concerning patients' psychiatric history, anthropometric measurements, medical comorbidities, surgical specifications and the use of antipsychotic drugs at the day of surgery were collected for analysis. Outcomes were gathered up to 24 months after surgery, except for weight loss for which data was collected up to 48 months after surgery. Retrospective data collection was approved by the Medical Ethics Committee of the Antwerp University Hospital (File code 15/48/513) and this study was performed in accordance with the latest version of the Helsinki Declaration.

Statistical Analysis

A mixed linear effects model was applied to determine the effects of antidepressants on the weight loss after RYGB surgery. In this analysis all weight loss registrations of all patients with at least one year of follow-up were inserted in a univariate and two multivariate models. In the univariate model, the individual influence of several patient and surgery related covariates on the weight loss after bariatric surgery, as well as the effect of continuous use of antidepressants during this first year, was determined. Subsequently, the influence of antidepressants on the %EBMIL and %TWL was determined in two multivariate models. In model 1, only patients undergoing primary bariatric surgery were included and all patients that underwent a revision of a previous bariatric procedure to a RYGB were excluded. Model 2 was not restricted to patients undergoing a primary bariatric procedure and thus also included patients undergoing revision surgery. In both models, patient- and surgery-related covariates with a significance level of $p<0.10$, as indicated in the univariate analyses, were selected as covariates for adjustment. Bivariate analysis of demographics and surgical characteristics were conducted using a Chi-squared statistic in case of categorical outcomes and a Student's t-test with LSD post-hoc testing for continuous outcomes as appropriate. Results are reported as either the mean %EBMIL or the estimated difference in %EBMIL/%TWL with 95% confidence interval (95%CI) in case of the mixed linear effects model or presented as the mean ±standard deviation (SD) and numbers with percentages for the demographics and surgical characteristics. All

statistical analyses were performed with SPSS (version 24, IBM, Chicago, IL). P-values of $p<0.05$ were considered statistically significant.

Results

Study cohort and baseline characteristics

In total, 751 patients were included in this study. For every of these patients, data concerning weight loss, psychiatric health and any treatment with antidepressants drugs were available at baseline and beyond the first year after the surgical procedure. Before surgery, patients had a mean BMI of 42.01 (±5.63) kg/m² and an age of 43.30 (±12.55) years. The majority of RYGB procedures was performed laparoscopically, with only 66 patients (8.79%) undergoing a primary open procedure (n=30) or being converted intraoperatively (n=36). Out of all patients included, 93 (12.38%) underwent a surgical revision to a RYGB due to unsatisfactory weight loss after a primary bariatric procedure. Failed gastric banding (n=60; 64.52%), Mason Gastroplasty (n=10; 10.75%) and biliopancreatic diversion-duodenal switch (n=10; 10.75%) were most frequently converted to a RYGB in this cohort.

A lifetime history of a psychiatric disorder was reported by 168 patients (22.37%), of which depression was the most frequently reported (n=142; 18.91%). Other psychopathologies frequently encountered in this study cohort were alcohol and substance abuse (n=22; 2.93%), personality disorders (n=12; 1.60%), anxiety disorders (n=11; 1.46%) and bipolar disorders (n=9; 1.20%).

At the moment of their operation, 125 patients (16.64%) were treated with at least one antidepressant drug. Of these 125 patients, 23 (18.40%) were treated with a combination therapy, totaling the amount of antidepressants prescribed to 148. Classes of antidepressants identified were: SSRI (n=79; 53.38%), SNRI (n=39; 26.35%), TCA (n=8; 5.41%), Trazodone (n=19; 12.84%), and NDRI (n=3; 2.03%). One year after the bariatric procedure, therapy status with antidepressants remained unchanged in 101 patients (80.80%), and was discontinued in 24 patients (19.20%). Baseline characteristics of patients not treated with antidepressants, patients with continued one-year use of antidepressants and those that discontinued use of antidepressants during the first postoperative year are displayed in table 1.

Weight loss and determinants of weight loss

Twelve months after the RYGB procedure, patients on average had lost 70.19 (±43.14) %EBMIL (28.41 ±%TWL). Weight loss further increased during the following months, with 77.38 (±30.10) %EBMIL (30.63 %TWL) at 24 months of follow up (Figure 1).

Higher age ($p<0.001$), a preoperative BMI above 40 kg/m² ($p<0.001$), primary open surgery or intra-procedural conversion to an open approach ($p=0.004$), type 2 diabetes ($p<0.001$) and revision surgery ($p<0.001$) were significantly associated with decreased %EBMIL after the RYGB and therefore included as covariates in the multivariate mixed linear effects models (Table 2). Although some antipsychotic drugs have been known to influence body weight, the use of antipsychotics was not associated with reduced weight loss.

Effects of treatment with antidepressants following the first year after RYGB surgery

In the univariate analysis of data, continuation of antidepressants during the first year after the RYGB was associated with significantly decreased %EBMIL (-2.81%) and %TWL (-1.36%) compared to patients not treated with antidepressants (Table 2 and Table 3). SNRIs (-7.72 %EBMIL, p<0.001) and TCAs (-15.36 %EBMIL, p<0.001) significantly decreased the observed weight loss (Table 4 and table 5). SSRIs, trazodone and NDRIs had no significant effect on the %EBMIL or %TWL.

Multivariate analysis confirmed the decreased weight loss in patients treated with antidepressants during the first year after their procedure (Table 2 and 3). Patients undergoing a primary RYGB (Model 1) lost significantly less %EBMIL (-2.86%, p=0.015) and %TWL (-0.89%, p=0.039) when therapy with antidepressants was continued. After addition of patients undergoing revision surgery to the analysis (Model 2), the difference in weight loss further increased (-5.52 %EBMIL, p<0.001). If antidepressants, on the other hand were discontinued shortly after the procedure and at least within the first year after the procedure, no significant effect on the %EBMIL or %TWL was observed. Again, only SNRIs (-12.47 %EBMIL, p<0.001) and TCAs (-15.27 %EBMIL, p=0.042) significantly reduced the weight loss achieved by patients in this first year after their RYGB (Table 4 and table 5).
While revision surgery itself was an important reason for less weight loss after the RYGB, the negative impact of several antidepressants on the %EBMIL and %TWL was more extensive in patients with a history of an earlier bariatric procedure.

Finally, to determine the influence of combination antidepressant therapy on the weight loss an additional multivariate model, including all classes of antidepressants and adjusting for covariates included in model 1 and 2, was constructed. In this model, no interaction between different classes of antidepressants was observed and SNRIs (-5.88 %EBMIL; 95%CI -9.39, -2.37; p<0.001) and TCAs (-12.84 %EBMIL; 95%CI -21.46, -4.23; p=0.003) remained significantly associated with decreased %EBMIL. Treatment with antidepressants was not associated with lower diabetes remission (p=0.302).

Long-term effects of treatment with antidepressants after RYGB surgery

Beyond 24 months, treatment with antidepressants remained associated with reduced efficiency of the RYGB in terms of weight loss: 36 months after surgery, patients had lost 4.83 %EBMIL (95%CI -7.52, -2.14; p<0.001) or 0.97 %TWL (95%CI -1.76, -0.19; p=0.015) less than untreated controls. SNRIs (-11.41 %EBMIL; 95%CI -15.27, -7.56; p<0.001) and TCAs (-13.24 %EBMIL; 95%CI -22.93, -3.54; p=0.007) were still associated with lower %EBMIL. Similarly, when investigating the outcomes up to 48 months after the RYGB, the %EBMIL achieved by patients on antidepressants was diminished with 3.54% (95%CI -6.06, -1.03; p=0.006). The %TWL was still reduced at that moment, but with a difference in %TWL of -0.74% (95%CI -1.50, -0.02; p=0.058) this result was not statistically significant. Although the effect of SNRIs (-10.19%, 95%CI -13.83 , -6.55; p<0.001) and TCAs (-9.23%, 95%CI -17.50 , -0.96; p=0.029) diminished over time, they remained predictive for lower %EBMIL up to 48 months after surgery.

Discussion

Weight gain is a frequent side effect of antidepressants and has been described, among others, in patients treated with paroxetine, amitriptyline, nortriptyline, duloxetine, and venlafaxine [10,12,13]. Therefore we investigated the potential influence of antidepressants on the weight loss after bariatric surgery in a large cohort of patients,

studying general, class- and antidepressant-specific outcomes after performing RYGB surgery. Our results demonstrated a 5.52 % reduction in %EBMIL and a 1.05% lower %TWL within the first 24 months after surgery. Even beyond 24 months, the difference in %EBMIL remained significant. As the effect of antidepressants on the body weight seems to depend on the mechanism of action of the antidepressant, the influence of SSRIs, SNRIs, TCAs, trazodone, and NDRIs on the weight loss after a RYGB was analyzed separately. In these analyses only SNRIs and TCAs were significantly associated with reduced weight loss up to 24 months after surgery.

To date, a limited number of studies have investigated the effect of antidepressants on weight loss after bariatric surgery [14,15]. In their study, Malone et al. could not demonstrate any effect of antidepressants within the first 12 months after surgery [15]. This study included a cohort of 364 patients, of whom 145 patients were treated with antidepressants at baseline. However, the majority of these patients (n=121, 83.45%) were taking SSRIs and 11 (7.59%) patients were treated with the NDRI Bupropion; the latter being one of the few antidepressants rather linked with weight loss [11]. Similarly, Love et al. also investigated the effects of antidepressant use on weight loss within the first 12 months after surgery [14]. Their study only included 48 patients taking antidepressants, and again the authors were unable to report class-specific effects of antidepressants.
Nevertheless, both studies had some important limitations. These studies were performed in relatively small numbers of patients samples, and with only 12 months of follow-up. Moreover, class- and drug-specific effects of antidepressants on the weight loss after bariatric surgery were not investigated in these studies. Yet, different mechanisms of action seem to be a major determinant of weight loss, as demonstrated by our results. Finally, adjustment or discontinuation of treatment with antidepressant drugs is frequent in the general population, and this is not different following bariatric surgery [9,16,17]. Unfortunately, both studies did not provide any data concerning the discontinuation of therapy. It is therefore unclear whether all included patients were treated with antidepressants during the entire duration of follow-up. Since our own results demonstrated no effect on the weight loss if therapy with antidepressants was discontinued within the first 12 months after surgery, inclusion of these patients in a study cohort could potentially mask the effect of prolonged antidepressant therapy, and could be the reason why these studies failed to observe a difference in weight loss.

The mechanisms, by which antidepressants cause weight gain or, in the case of bariatric surgery reduce weight loss, are presumed to be multifactorial and depend on the mechanism of action of each specific antidepressant. To date, several serotonin receptors have been identified and these receptors generally are associated with appetite regulation, food intake and eating behaviors [18]. Other antidepressants, including amitriptyline, sertraline and trazodone antagonize the alpha-1 adrenergic receptor, increasing appetite and reducing energy consumption [18]. Antihistaminic effects of some antidepressants and reduced energy expenditure due to sedative effects may affect the body weight as well [19]. For many antidepressants the precise mechanism by which weight gain is caused, remains unknown. Another factor that should be considered is the effect of psychiatric disorders on the long-term weight loss after bariatric surgery. Although our study could not associate psychiatric disorders with diminished postoperative weight loss, some studies did demonstrate decreased weight loss in patients with certain mental health disorders [8,5,6]. Finally, changes in pharmacokinetics of some antidepressants following bariatric surgery have been described, and thus can potentially influence weight loss.

Although the differences in %EBMIL and %TWL in patients taking antidepressants appear to be modest, these observations do have some clinical significance. To begin with, our results clearly demonstrate the effect of

antidepressants on the weight loss to be very heterogeneous. SSRIs and Trazodone had no effect on the %EBMIL or %TWL after the RYGB procedure. Therefore, patients treated with these drugs can be reassured their weight loss will not be influenced and these drugs can be continued without any concern for the outcomes after surgery. SNRIs and TCAs on the other hand, did clearly influence the weight loss and the %EBMIL was reduced with up to 12.47% when also including patients undergoing revision surgery. Some individual drugs belonging to these classes of antidepressants even further reduced outcomes. Therefore, when looking at the effects of antidepressants on bariatric surgery outcomes, the class-effect determined by the mechanism of action rather than just the fact whether a patient is treated or not treated with antidepressants, should be considered.
Additionally, several investigated covariates like increasing age, higher BMI, revision surgery and open surgery seem to be associated with reduced weight loss after surgery. In combination with these covariates, antidepressants could be decisive whether the weight loss is sufficient or insufficient.

Although this study investigated the role of several antidepressants on the weight loss after RYGB surgery in a large study cohort with obligatory follow-up during at least the first 12 months after surgery, some limitations have to be considered when interpreting the results.
Firstly, because this was a retrospective study, data collection was restricted to the data available in the medical records. Therefore we opted to only include patients with thorough and complete follow-up for at minimum 12 months, and with antidepressant therapy, psychiatric health status and weight loss fully documented. This criterion prevented confounding due to unreported self-discontinuation of therapy or changes in therapy ,and ensured full follow-up. Potentially, this requirement could have caused a bias by itself, because patients with unsatisfactory weight loss, mental instability and bad therapy compliance are more likely to miss appointments and thus being excluded from this study. Furthermore, as discontinuation or modification of antidepressant therapy have been described to occur often after bariatric surgery, the sample size of patients continuously being treated with antidepressants during the first year after surgery was reduced with 19.20% in the current study [8]. As a result, after stratification of patients corresponding to the type of antidepressant taken, the number of patients and weight loss outcomes in some of the groups importantly decreased. Especially for detecting the effect of NDRIs this study had insufficient power. However, because NDRIs like bupropion are rather associated with weight loss than weight gain, we did not expect to observe any effect before the start of this study.
We primarily analyzed the effects of 12-month therapy with antidepressants on the weight loss after RYGB surgery up to 24 months after surgery, but extended our analysis up to 48 months after surgery. Ideally we would have preferred to analyze the effects of antidepressants beyond 48 months. However, when time after surgery advances, the influence of many lifestyle factors including, modifications in diet, decreasing dietary compliance, changes in activity levels and drug therapy, on the body weight start to increase. Heterogeneity in medical and mental health, inborn metabolism and the genetic background also could become more significant and attribute to differences in long-term outcomes after bariatric surgery [20,21]. We therefore consider our results beyond 24 months after surgery mostly indicative of an effect of antidepressants on the weight loss after bariatric surgery.

In surgical practice, given that our results demonstrate SSRIs and trazodone to be weight neutral in RYGB patients, and this up to 48 months after surgery, these classes of antidepressants can therefore be safely continued after RYGB surgery. SNRIs and TCAs on the other hand do significantly decrease weight loss after surgery. Ideally, these drugs would be discontinued after bariatric surgery or switched to another type of antidepressant.

However, this seems far from ideal and not always an option as switching between classes requires tapering and guidelines advise long-term treatment to prevent a relapse [22,23]. In patients already receiving long term treatment and with limited indication for continuation of the antidepressant therapy, our study demonstrates discontinuation of therapy to be beneficial.

Conclusion

This study demonstrated an association between continuous treatment with antidepressants during the first year after a RYGB procedure and decreased %EBMIL and %TWL. After analyzing the effect of different classes of antidepressants on the weight loss after surgery, only SNRIs and TCAs were importantly responsible for lower weight loss. These effects continued to be visible even beyond 48 months after the RYGB. When clinically possible to discontinue these drugs or to switch to an SSRI or trazodone, this could have marked influence on the weight loss. Because of the multifactorial aspects of weight loss after bariatric surgery and because of the large amount of antidepressants marketed worldwide, large prospective cohort studies that investigate the mechanisms of action in which these specific antidepressants act on postoperative weight loss after bariatric surgery, are required.

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Compliance with Ethical Standards

Conflict of interest: Philip Plaeke declares that he has no conflict of interest, Filip Van Den Eede declares that he has no conflict of interest, Ben Gys declares that he has no conflict of interest, Anthony Beunis declares that he has no conflict of interest, Martin Ruppert declares that he has no conflict of interest, Joris De Man declares that he has no conflict of interest, Benedicte De Winter declares that she has no conflict of interest, Guy Hubens declares that he has no conflict of interest.

Ethical 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. Retrospective data collection was approved by the ethical committee of the Antwerp University Hospital (File number 15/48/513).

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Tables

Table 1: Comparison of baseline demographic and surgical characteristics between patients treated (n=125) and not treated with antidepressants (n=626)

	No Antidepressant group (n= 626)	Continued (>12 months) use of antidepressants (n= 101)	Antidepressants discontinued within 12 months after surgery (n= 24)	p-value[1]
Mean Age (SD)	42.59 (12.75)	48.14 (10.36)	41.58 (11.62)*	<0.001
Mean Baseline weight (kg, SD)	119.69 (20.12)	115.06 (19.63)	121.03 (23.22)	0.079
Mean Baseline BMI (SD)	41.96 (5.49)	41.95 (5.60)	43.65 (8.68)	0.564
Male Gender (%)	217 (34.66)	16 (15.84)	3 (12.50)	<0.001
Revision surgery (%)	75 (11.98)	13 (12.87)	5 (20.83)	0.453
Open Surgery (%)	48 (7.67)	15 (14.85)	3 (12.50)	0.015
Type 2 diabetes (%)	162 (25.88)	34 (33.66)	3 (12.50)*	0.389
BMI above 40 kg/m² (%)	390 (62.30)	56 (55.45)	15 (62.5)	0.249
Age above 40 years (%)	285 (45.53)	62 (61.39)	9 (37.50)*	0.021
Psychiatric history (%)	75 (11.98)	99 (98.02)	23 (95.83)	<0.001
Use of Antipsychotics (%)	8 (1.28)	23 (22.77)	1 (4.17)*	<0.001

Outcomes are expressed as the mean with standard deviation (SD) or the number of patients (%) fulfilling the characteristic in every group. [1] Reported p-values represent the statistical difference between patients belonging to the no antidepressant and antidepressant groups. Differences between groups were analyzed with a student's t-test (with LSD post-hoc testing) or chi-square test when appropriate. *indicates significant difference at the $p<0.05$ level between patients that continued their antidepressants during the first year after the RYGB and those whose medication was discontinued.

Table 2: Univariate and multivariate effects of antidepressants and several covariates on the **%EBMIL** after RYGB surgery (Mean Difference %EBMIL [95% Confidence Interval]).

Parameter	Unadjusted outcomes [95%CI]	P-value	Model 1 [95%CI]	P-value	Model 2 [95%CI]	P-value
>1 year therapy with antidepressants	**-2.81 [-5.26 , -0.36]**	**0.025**	**-2.86 [-5.17 , 0.56]**	**0.015**	**-5.52 [-8.45 , -2.60]**	**<0.001**
Antidepressants stopped	1.42 [-3.39 , 6.22]	0.563	-0.14 [-4.63 , 4.35]	0.950	2.92 [-2.40 , 8.24]	0.281
Male Gender	1.18 [-0.66 , 3.01]	0.210	Not included in model 1		Not included in model 2	
Age (/year)	**-0.14 [-0.21 , -0.07]**	**<0.001**	**-0.19 [-0.26 , -0.11]**	**<0.001**	**-0.26 [-0.35 , -0.18]**	**<0.001**
BMI >40 kg/m²	**-14.02 [-15.75 , -12.30]**	**<0.001**	**-15.49 [-17.23 , -13.76]**	**<0.001**	**-14.45 [-16.61 , -12.30]**	**<0.001**
Open Surgery	**-5.40 [-9.06, -1.74]**	**0.004**	-3.29 [-6.74 , 0.16]	0.061	**-12.31 [-16.18 , -8.46]**	**<0.001**
Pos. Psychiatric History	-0.41 [-2.46 , 1.64]	0.696	Not included in model 1		Not included in model 2	
Anti-Psychotics	-1.56 [[-5.59 , 2.46]	0.447	Not included in model 1		Not included in model 2	
Type 2 Diabetes	**-3.20 [-5.10 , -1.29]**	**0.001**	**-3.43 [-5.33 , -1.52]**	**<0.001**	-2.08 [-4.50 , 0.34]	0.091
Revision Surgery	**-14.73 [-17.92 , -11.54]**	**<0.001**	Not included in model 1		**-16.76 [-19.93 , -13.60]**	**<0.001**

95%CI, 95% Confidence Interval; BMI, Body Mass Index; %EBMIL, % Excessive BMI Loss; Pos., Positive. Results are reported as the observed difference in %EBMIL with 95% confidence interval compared to patients not treated with antidepressants or without the indicated parameter. Covariates adjusted for in model 1: age, open surgery, type 2 diabetes mellitus and BMI. In model 2, adjustment was performed for the same variables of model 1. However, as patients that underwent a revision to a RYGB were included in this analysis, revision surgery was added as a covariate to this mixed linear effects model.

Table 3: Univariate and multivariate effects of antidepressants and several covariates on the **%TWL** after RYGB surgery (Mean Difference %TWL [95% Confidence Interval]).

Parameter	Unadjusted outcomes [95%CI]	P-value	Model 1 [95%CI]	P-value	Model 2 [95%CI]	P-value
>1 year therapy with antidepressants	**-1.36 [-2.20 , -0.51]**	**0.002**	**-0.89 [-1.74 , -0.05]**	**0.039**	**-1.05 [-1.87 , -0.23]**	**0.012**
Antidepressants stopped	0.53 [-1.13 , 2.19]	0.528	-0.03 [-1.66 , 1.60]	0.972	0.78 [-0.72 , 2.28]	0.309
Male Gender	-0.34 [-0.98 , 0.30]	0.300	Not included in model 1		Not included in model 2	
Age (/year)	**-0.11 [-0.14 , -0.09]**	**<0.001**	**-0.09 [-0.12 , -0.07]**	**<0.001**	**-0.11 [-0.13 , -0.08]**	**<0.001**
BMI >40 kg/m²	**0.75 [0.12 , 1.39]**	**0.020**	0.19 [-0.44 , 0.83]	0.549	0.56 [-0.05 , 1.17]	0.072
Open Surgery	-1.23 [-2.50 , 0.04]	0.057	-0.50 [-1.76 , 0.76]	0.439	**-1.37 [-2.46 , -0.28]**	**0.014**
Pos. Psychiatric History	-0.58 [-1.29 , 0.13]	0.108	Not included in model 1		Not included in model 2	
Anti-Psychotics	-0.73 [-2.12 , 0.67]	0.307	Not included in model 1		Not included in model 2	
Type 2 Diabetes	**-2.18 [-2.84 , -1.52]**	**<0.001**	**-1.24 [-1.94 , -0.54]**	**0.001**	-0.50 [-1.19 , 0.19]	0.159
Revision Surgery	**-6.05 [-6.92 , -5.19]**	**<0.001**	Not included in model 1		**-5.88 [-6.77 , -4.99]**	**<0.001**

95%CI, 95% Confidence Interval; BMI, Body Mass Index; %TWL, % Total Weight Loss; Pos., Positive. Results are reported as the observed difference in %TWL with 95% confidence interval compared to patients not treated with antidepressants or without the indicated parameter. Covariates adjusted for in model 1: age, open surgery, type 2 diabetes mellitus and BMI. In model 2, adjustment was performed for the same variables of model 1. However, as patients that underwent a revision to a RYGB were included in this analysis, revision surgery was added as a covariate to this mixed linear effects model.

Table 4: Effects of different types of antidepressants subgroups on the **%EBMIL** during the first year after RYGB surgery, determined in unadjusted and adjusted mixed linear effects models (Mean Difference %EBMIL [95% Confidence Interval])

	Unadjusted outcomes	Model 1	Model 2
Continuous use of Antidepressants			
Overall effect of antidepressants	**-2.81 [-5.26 , -0.36]***	**-2.86 [-5.17 , 0.56]***	**-5.52 [-8.45 , -2.60]#**
SSRI	**1.47 [-1.25 , 4.19]**	**-0.22 [-2.77 , 2.33]**	**0.46 [-2.74 , 3.67]**
Paroxetine	3.33 [-2.15 , 8.81]	4.02 [-1.13 , 9.18]	3.01 [-2.96 , 8.97]
Citalopram	-5.06 [-13.30 , 3.19]	-3.97 [-11.70 , 3.76]	-7.47 [-17.59 , 2.65]
Escitalopram	2.99 [-1.80 , 7.78]	-2.11 [-6.59 , 2.38]	-3.20 [-9.27 , 2.88]
Fluoxetine	-2.08 [-9.17 , 5.00]	-3.41 [-10.09 , 3.28]	2.48 [-2.57 , 10.54]
Sertraline	2.50 [-2.73 , 7.72]	1.46 [-3.43 , 6.34]	3.24 [-2.88 , 9.37]
SNRI	**-7.72 [-11.36 , 4.08]#**	**-6.45 [-9.85 , -3.05]#**	**-12.47 [-16.63 , -8.30]#**
Duloxetine	-6.49 [-11.63 , -1.35]*	-7.26 [-12.07 , -2.46]*	-21.23 [-26.98 , -15.48]#
Venlafaxine	-8.89 [-13.89 , -3.88]#	-5.67 [-10.36 , -0.98]*	-3.80 [-9.56 , 1.97]
TCA	**-15.36 [-24.48 , -6.24]#**	**-15.27 [-23.74 , -6.79]#**	**-11.01 [-21.65 , -0.38]***
Amitriptyline	-24.60 [-35.47 , -13.73]#	-20.65 [-30.77 , -10.54]#	-16.05 [-28.04 , -4.05]*
Nortriptyline	-10.78 [-31.96 , 10.39]	-19.57 [-39.62 , 0.49]	-14.01 [-50.67 , 22.65]
Trazodone	**-0.99 [-6.37 , 4.40]**	**0.48 [-4.60 , 5.57]**	**-2.10 [-8.36 , 4.15]**
NDRI	**-0.54 [-12.70 , 11.63]**	**-4.02 [-15.70 , 7.66]**	**5.06 [-10.52 , 20.63]**
Antidepressants stopped within 12 months after surgery	**0.53 [-1.13 , 2.19]**	**-0.03 [-1.66 , 1.60]**	**0.78 [-0.72 , 2.28]**

SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Selective Serotonin and Norepinephrine Reuptake Inhibitors; TCA, Tricyclic Antidepressants; NDRI, Norepinephrine and Dopamine Reuptake Inhibitors. Overview of the effect of antidepressants on the %EBMIL after RYGB surgery. Results are expressed as the difference in mean %EBMIL [95% confidence interval] and are compared to patients not treated with antidepressants at the time of surgery. Variables adjusted for in model 1: age, open surgery, type 2 diabetes mellitus and BMI. Model 2 included patients that underwent a revision to a RYGB and adjusts for all variables of model 1 and revision surgery. * indicates $p<0.05$. # indicates $p\leq0.001$.

Table 5: Effects of different types of antidepressants subgroups on the **%TWL** during the first year after RYGB surgery, determined in unadjusted and adjusted mixed linear effects models (Mean Difference %TWL [95% Confidence Interval])

	Unadjusted outcomes	Model 1	Model 2
Continuous use of Antidepressants			
Overall effect of antidepressants	**-1.36 [-2.20 , -0.51]***	**-0.89 [-1.74 , -0.05]***	**-1.05 [-1.87 , -0.23]***
SSRI	**-0.32 [-1.26 , 0.63]**	**-0.15 [-1.09 , 0.78]**	**-0.39 [-1.29 , 0.51]**
Paroxetine	0.68 [-1.24 , 2.60]	1.23 [-0.68 , 3.12]	-0.09 [-1.83 , 1.64]
Citalopram	-2.81 [-5.68 , 0.06]	-2.16 [-5.04 , 0.73]	-2.58 [-5.49 , 0.34]
Escitalopram	-0.90 [-2.54 , 0.74]	-0.94 [-2.57 , 0.69]	-0.76 [-2.47 , 0.96]
Fluoxetine	-0.91 [-3.40 , 1.59]	-1.20 [-3.65 , 1.25]	-0.02 [-2.26 , 2.22]
Sertraline	0.82 [-0.99 , 2.63]	0.93 [-0.85 , 2.71]	0.24 [-1.46 , 1.94]
SNRI	**-2.20 [-3.46 , -0.94]#**	**-1.92 [-3.17 , -0.68]***	**-1.45 [-2.63 , -0.27]***
Duloxetine	-2.24 [-4.03 , -0.45]*	-1.47 [-3.24 , 0.30]	-1.68 [-3.32 , -0.03]*
Venlafaxine	-2.17 [-3.89 , -0.45]*	-2.35 [-4.06 , -0.64]*	-1.23 [-2.85 , 0.40]
TCA	**-4.40 [-7.57 , -1.23]***	**-4.36 [-7.44 , -1.28]***	**-1.94 [-4.86 , 0.99]**
Amitriptyline	-6.49 [-10.29 , -2.69]#	-6.84 [-10.53 , -3.15]#	-3.19 [-6.60 , 0.22]
Nortriptyline	-5.32 [-12.72 , 2.07]	-4.62 [-12.02 , 2.78]	-4.09 [-11.38 , 3.20]
Trazodone	**0.58 [-1.29 , 2.45]**	**1.18 [-0.67 , 3.03]**	**-0.24 [-1.99 , 1.52]**
NDRI	**0.28 [-3.93 , 4.49]**	**0.38 [-3.86 , 4.61]**	**1.68 [-2.65 , 6.01]**
Antidepressants stopped within 12 months after surgery	**0.53 [-1.13 , 2.19]**	**-0.03 [-1.66 , 1.60]**	**0.78 [-0.72 , 2.28]**

SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Selective Serotonin and Norepinephrine Reuptake Inhibitors; TCA, Tricyclic Antidepressants; NDRI, Norepinephrine and Dopamine Reuptake Inhibitors. Overview of the effect of antidepressants on the %TWL after RYGB surgery. Results are expressed as the difference in mean %TWL [95% confidence interval] and are compared to patients not treated with antidepressants at the time of surgery. Variables adjusted for in model 1: age, open surgery, type 2 diabetes mellitus and BMI. Model 2 included patients that underwent a revision to a RYGB and adjusts for all variables of model 1 and revision surgery. * indicates $p<0.05$. # indicates $p\leq0.001$.

Figure Legend

Fig. 1 Evolution of the weight loss following gastric bypass surgery dependent on the treatment status with antidepressants. Weight loss is displayed up to 24 months after surgery and expressed as the percentage excess BMI loss (%EBMIL, a) or percentage total weight loss (%TWL, b). Red line, no treatment with antidepressants; blue line, treatment with antidepressants.