



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

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Abstract

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

Methods Patients with a fully documented antidepressant treatment status for at least 12 months were retrospectively included. Weight loss was expressed as the percentage excess BMI loss (%EBMIL) or percentage total weight loss (%TWL). A mixed linear effects model was used to determine the impact of continued and discontinued 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. No significant effects of antidepressants on metabolic outcomes after surgery were observed.

Conclusions Treatment with antidepressants was associated with reduced weight loss after gastric bypass surgery, but only if treatment was continued for at least 1 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

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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-norepinephrine reuptake inhibitor
TCA	Tricyclic antidepressant
NDRI	Norepinephrine and dopamine reuptake inhibitor
95%CI	95% confidence interval
SD	Standard deviation
HDL	High-density lipoprotein

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 loss 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 2 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 2 years after the surgical intervention.

Materials and methods

Study population

Of all patients who underwent bariatric surgery in the Antwerp University Hospital between January 2008 and January 2017, patients undergoing an 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 (Table 1). As this study aimed to determine the effects of continuous antidepressant treatment during the first 12 months after an RYGB, full electronic patient records containing the medical treatment and therapy with antidepressants at the time of the procedure and 1 year later were required. Patients' mental health status was routinely assessed in preoperative semi-structured interviews conducted at our hospital's psychiatry department.

All gastric bypass procedures were performed using the same technique, constructing an alimentary limb of approximately 100–120 cm and biliopancreatic limb with a length of approximately 50–70 cm. Patients received standard dietary instructions and were routinely followed by an in-hospital dietitian.

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 treatment status or who underwent a bariatric procedure other than the RYGB, were 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 percentage total weight loss (%TWL). For every patient, the use of antidepressants at the time of surgery and 1 year later was registered. Antidepressants were divided into five classes based upon their mechanism of action: selective

Table 1 Overview of the inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Patients undergoing Roux-en-Y gastric bypass between January 2008 and January 2017. • BMI ≥ 35 kg/m² with comorbidities (diabetes, obstructive sleep apnea syndrome, therapy-resistant arterial hypertension) or a BMI ≥ 40 kg/m² in the absence of comorbidities • Conversion from failed gastric banding or Mason gastroplasty or biliopancreatic diversion with duodenal switch and a BMI ≥ 35 kg/m² • Fully documented antidepressant treatment status before surgery and during the first 12 months after surgery • Patients belonging to the following groups: <ul style="list-style-type: none"> - Continuous 1-year use of antidepressants - Antidepressants stopped within 12 months after surgery - No antidepressants before and during the first 12 months after surgery • Treatment with SSRIs, SNRIs, TCAs, NDRIs, or trazodone • ≥ 12 months of in-hospital follow-up 	<ul style="list-style-type: none"> • Patients undergoing sleeve gastrectomy or gastric banding • Unknown antidepressant treatment status • Patients belonging to the following groups: <ul style="list-style-type: none"> - Antidepressants started after surgery in a patient that was not on treatment with antidepressants before surgery. - Major modifications to the antidepressant treatment during follow-up • Treatment with other antidepressants • Missing preoperative evaluation, external follow-up, ≤ 12 months in-hospital follow-up

BMI, body mass index; *SSRIs*, selective serotonin reuptake inhibitors; *SNRIs*, serotonin-norepinephrine reuptake inhibitors; *TCAs*, tricyclic antidepressants; *NDRIs*, norepinephrine and dopamine reuptake inhibitors

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 was collected. Outcomes were gathered up to 24 months after surgery, except for weight loss for which data was collected up to 48 months after surgery. All outcomes are exclusively based on office visits and in-hospital measurements. Diabetes remission was defined in accordance with the American Diabetes Association definition. Data collection was exclusively based on hospital visits and retrospective data collection was approved by the Medical Ethics Committee of the Antwerp University Hospital (File code 15/48/513). This study was performed in accordance with the latest version of the Helsinki Declaration.

Formulas

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

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

Statistical analysis

Before data collection, a sample size calculation for the main research question ("effects of antidepressants on %EBMIL after gastric bypass surgery") was performed using preliminary data. A minimal sample size of 472 patients, with an allocation of 393 patients to the "no antidepressant group" and 79 patients to the "antidepressant group," was deemed necessary to achieve 80% power at 12 months postoperatively. Nevertheless, to maximize the power of the secondary research questions and to make the mixed linear model more reliable, the number of included patients was increased.

A mixed linear effects model was applied to determine the effects of antidepressants on weight loss after RYGB surgery. In this analysis, all weight loss registrations of all patients with

at least 1 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 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, solely patients undergoing primary bariatric surgery were included. Model 2 was not restricted to patients undergoing a primary bariatric procedure and also included patients undergoing revision surgery. In both models, patient- and surgery-related covariates with a significance level of $p < 0.10$, as indicated by univariate analysis, were selected as covariates for adjustment. Bivariate analysis of demographics and surgical characteristics was conducted using a chi-squared test in case of categorical outcomes and Student's *t* test with LSD post hoc test for continuous outcomes. Results are reported as either the mean %EBMIL or the estimated difference in %EBMIL/%TWL with a 95% confidence interval (95%CI) in case of a mixed linear effects model. Patient demographics and surgical characteristics are presented as the mean \pm standard deviation (SD), absolute number, or percentage. 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

Of all patients who underwent an RYGB between January 2008 and January 2017, 751 patients (53.0%) met the inclusion and exclusion criteria. Main reasons for exclusion were incomplete follow-up due to follow-up elsewhere and missing information concerning antidepressant use. For every included patient, data concerning weight loss, psychiatric health, and treatment with antidepressants drugs were available at baseline and beyond the first year after the surgical procedure.

At the time of surgery, patients had a mean BMI of 42.01 (± 5.63) kg/m² and mean age of 43.30 (± 12.55) years. The majority of RYGB procedures were performed laparoscopically, with only 66 patients (8.79%) undergoing a primary open procedure ($n = 30$) or being converted intraoperatively ($n = 36$). Ninety-three patients (12.38%) underwent a surgical revision to an RYGB due to unsatisfactory weight loss after a primary bariatric procedure. Failed gastric banding ($n = 60$; 64.52%), Mason gastropasty ($n = 10$; 10.75%), and biliopancreatic diversion-duodenal switch ($n = 10$; 10.75%) were most frequently revised to an RYGB.

A lifetime history of a psychiatric disorder was reported by 168 patients (22.37%), of which depression was the most frequent ($n = 142$; 18.91%). Other psychopathologies

regularly 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 combination therapy, totaling the number of antidepressants prescribed to 148. Classes of antidepressants identified were as follows: 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, treatment with antidepressants remained unchanged in 101 patients (80.80%) and was discontinued in 24 patients (19.20%).

Furthermore, treatment with antidepressants was not associated with a higher baseline prevalence of diabetes type II ($p = 0.389$), arterial hypertension ($p = 0.146$), or liver steatosis ($p = 0.370$). However, lipid levels were statistically higher, with patients on antidepressants having a higher tendency to have dyslipidemia (Table 2). Complete baseline characteristics of patients not treated with antidepressants, patients with 1-year use of antidepressants, and those that discontinued antidepressants during the first postoperative year are presented in Table 2.

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 \pm %TWL). Weight loss further increased during the following months, with 77.38 (± 30.10) %EBMIL (30.63 %TWL) at 24 months of follow up (Fig. 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 3). Although some antipsychotic drugs have been known to influence body weight, treatment with antipsychotics was not associated with reduced weight loss in this cohort.

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

In the univariate analysis of data, the continuation of antidepressants during the first year after the RYGB was associated with significantly decreased %EBMIL (-2.81%) and %TWL (-1.36%) compared with patients not treated with antidepressants (Table 3 and Online Resource 1). SNRIs (-7.72% %EBMIL, $p < 0.001$) and TCAs (-15.36% %EBMIL, $p < 0.001$) significantly decreased weight loss (Table 4 and

Table 2 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
Liver steatosis (%)	445 (71.09%)	74 (73.27)	19 (79.17)	0.370
Med. total cholesterol (mg/dl, IQR)	189 (51.75)	198 (48.50)	199 (49.00)	0.009
Med. triglycerides (mg/dl, IQR)	140 (90.75)	156 (107.50)	117 (122.00)	0.026
Med. HDL (mg/dl, IQR)	45.00 (18.00)	48.00 (17.50)	52 (24.00)	0.007
Arterial hypertension (%)	241 (38.62)	45 (44.55)	12 (50.00)	0.146
BMI above 40 kg/m ² (%)	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

HDL, high-density lipoprotein; Med., median; IQR, interquartile range. 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), Mann-Whitney U test, 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

Online Resource 2). 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 3 and Online Resource 1). Patients undergoing a primary RYGB (model 1) lost significantly less %EBMIL (-2.86% , $p = 0.015$) and %TWL (-0.89% , $p = 0.039$) if treatment with antidepressants was continued. After including patients undergoing revision surgery to the analysis (model 2), the difference in weight loss further increased (-5.52% %EBMIL, $p < 0.001$). On the other hand, when antidepressants 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 weight loss achieved by patients in this first year after their RYGB (Table 4 and Online Resource 2).

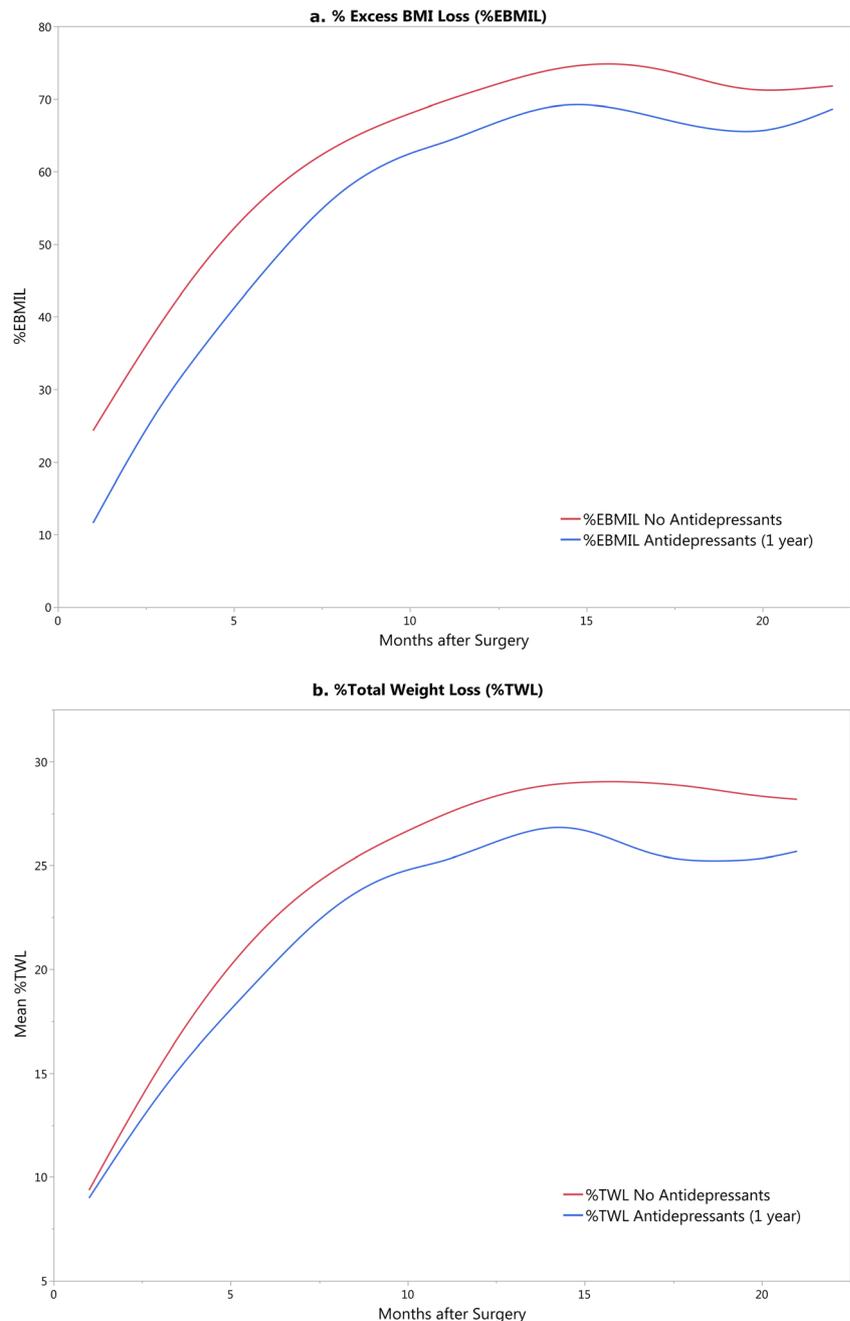
While revision surgery itself was an important reason for less weight loss after the RYGB, the negative impact of

several antidepressants on the %EBMIL and %TWL was more extensive in patients with a history of an earlier bariatric procedure.

To determine the influence of combination antidepressant therapy on the weight loss, an additional multivariate model was constructed, which included all classes of antidepressants and adjusted for all covariates of models 1 and 2. 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. The severity of depression or the number of antidepressants used for treatment ($p = 0.531$) was not associated with reduced weight loss.

Finally, although antidepressants were associated with reduced weight loss, this was not reflected in statistically significant differences in metabolic outcomes. Complete diabetes remission was more often reached in patients not treated with antidepressants at baseline (61.5% versus 50.0%), but this difference was not statistically significant ($p = 0.302$).

Fig. 1 Evolution of the weight loss following gastric bypass surgery depending 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



Similarly, although triglyceride levels ($p=0.010$) and total cholesterol levels ($p=0.002$) remained significantly higher in patients treated with antidepressants, the reduction in lipid levels compared with baseline levels was not influenced by antidepressant use.

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; $p =$

Table 3 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/m ²	- 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 mean %EBMIL with a 95% confidence interval compared with patients not treated with antidepressants or without the indicated parameter (italicized values). Covariates adjusted for in model 1: age, open surgery, type 2 diabetes mellitus, and BMI. In model 2, an adjustment was performed for the same variables as in model 1. However, as patients that underwent a revision to an RYGB were included in this analysis, revision surgery was added as a covariate to this mixed linear effects model

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 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 NDRI on the weight loss after an 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 antidepressants. It is

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	1.42 [- 3.39, 6.22]	- 0.14 [- 4.63, 4.35]	2.92 [- 2.40, 8.24]

SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-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 with patients not treated with antidepressants at the time of surgery (italicized values). Variables adjusted for in model 1: age, open surgery, type 2 diabetes mellitus, and BMI. Model 2 included patients that underwent a revision to an RYGB and adjusts for all variables of model 1 and revision surgery

*Indicates $p < 0.05$

Indicates $p \leq 0.001$

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 when treatment 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 this 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 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 [5, 6, 8]. In addition, changes in the pharmacokinetics of some antidepressants following bariatric surgery have been described, and thus can potentially influence weight loss [20].

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 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 significantly influenced and these drugs can be continued without any concern for the outcomes after surgery. On the other hand, SNRIs and TCAs 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 attribute to insufficient weight loss.

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 be safely continued after RYGB surgery. Conversely, SNRIs and TCAs 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 relapse [21, 22]. In patients already receiving long-term treatment with antidepressants and with a limited indication for the continuation of therapy, our study demonstrates discontinuation of therapy to be beneficial.

Although this study investigated the role of several antidepressants on 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.

To begin with, 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 least 12 months, and with antidepressant therapy, psychiatric health status, and weight loss fully documented. This criterion prevented confounding and methodological errors due to unreported self-discontinuation of therapy or changes in therapy and ensured full follow-up. However, this requirement could have introduced a selection 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. Although we cannot be absolutely certain that patients lost to follow-up were fully comparable with patients that were included in this study, analysis of preoperative parameters did not reveal any significant difference between these patients. Active psychopathological condition ($p = 0.626$), lifetime history of psychopathology ($p = 0.929$), antidepressant therapy ($p = 0.438$), and depression ($p = 0.995$) were comparable in both groups. Nevertheless, our strict inclusion and exclusion criteria caused 47% of patients to be excluded because of incomplete data at 12 months. As patients underwent bariatric surgery in a university

hospital, which also acts as a tertiary referral center, the main reason for exclusion was follow-up elsewhere (other hospital, private practice, general practitioner) after initial follow-up in our center. This is also reflected in the percentage of patients with complete data based on office visits at 24 months (66.1%). Nevertheless, because the mixed linear model was based on over 5800 different data collection points, the statistical power of the main research question was not compromised.

Furthermore, as discontinuation or modification of antidepressant therapy has 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 based on the class of antidepressant, the number of patients and weight loss outcomes in some of the groups importantly decreased. Especially for detecting the effect of NDRI this study had insufficient power. However, because NDRI 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.

Similarly, although antidepressants seemed associated with less weight loss after an RYGB, this had no observed influence on metabolic outcomes. Moderately lower complete diabetes remission rates were seen in patients treated with antidepressants. However, this difference was not statistically significant. Unfortunately, the required sample size to fully study the impact on metabolic outcomes was not reached. Potentially, the metabolic effects of TCAs and SNRIs could be clinically relevant, as these drugs were associated with a considerate reduction of weight loss. This should, however, be confirmed in larger cohort studies.

Additionally, we primarily analyzed the effects of a 12-month treatment with antidepressants on the weight loss 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 influence long-term outcomes after bariatric surgery [23, 24]. Therefore, we consider our results beyond 24 months after surgery mostly indicative of an effect of antidepressants on the weight loss after bariatric surgery.

Finally, in this study, we opted to solely include patients that underwent an RYGB. Although we could have added patients that underwent a sleeve gastrectomy, we argued that due to the relative recentness of this procedure in our center, the sample size of this group would be too small to achieve sufficient power. Furthermore, as the mechanisms of action of

RYGB and sleeve gastrectomy procedures are presumed to be different to some extent, the alternative of pooling of these patients together with the RYGB cohort would presumably have increased heterogeneity. Nevertheless, both procedures were similar in terms of preoperative patient characteristics and psychological factors. As sleeve gastrectomy is becoming more and more standard, it would be interesting to investigate in future studies whether antidepressant use is also associated with a reduction in weight loss after this procedure.

Conclusion

This retrospective study demonstrated an association between continuous treatment with antidepressants during the first year after an RYGB procedure and decreased %EBMIL and %TWL. After analyzing the effect of different classes of antidepressants on weight loss after surgery, only SNRIs and TCAs were importantly associated with reduced weight loss. These effects continued to be visible even beyond 48 months after the RYGB. Because of the complexity of the interaction of antidepressants with weight loss and bariatric surgery, it is uncertain which underlying mechanisms cause this diminished weight loss. Nevertheless, when clinically possible to discontinue these drugs or to switch to an SSRI or trazodone, this could potentially influence weight loss. Since weight loss after bariatric surgery is multifactorial and because of the large number 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 The authors declare that they have 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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