



Mood Disorders and Bariatric Surgery Patients: Pre- and Post- Surgery Clinical Course- An Overview

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Abstract

Aim: The purpose of the study was to evaluate the clinical course before and after bariatric surgery (BS) of patients affected by mood disorders as Major Depressive Disorder (MDD) and Bipolar Disorder (BD).

Methods: A search in Pubmed's medline was performed for English-spoken articles published from January 2000 to May 2015 using the keywords 'depression', 'bipolar disorder', 'mood disorders' and 'antidepressive drugs' combined with 'bariatric surgery' and 'obesity surgery'. A total of 43 studies was evaluated.

Results: Patients candidates to BS were frequently affected by MDD or BD. A substantial modification of psychopathology after surgery was reported both in the short and long follow up. BS shows important effects on metabolism of psychotropic drugs.

Conclusions: Careful preoperative assessment and close monitoring post-surgery are recommended.

Keywords

Depression, Bipolar disorder, Mood disorders, Psychotropic drugs, Bariatric surgery

a common etiology between obesity and depression for several reasons: unhealthy diets that include energy dense foods promote the development of both pathologies, reduced physical activity and sedentary lifestyle are commonly described in obese and depressed patients, impaired sleep and/or circadian cycles damage mood and increase body weight, recurrent psychological stress and early life trauma seem to contribute to a late-onset obesity and depression [4].

People with Bipolar Disorder (BD) also present a higher prevalence of overweight (BMI 25.0-29.9), generalized obesity (BMI \geq 30.0), and central obesity, when compared with the general population [5]. The elevated rate of obesity is a risk factor for cardiovascular disease, the most common cause of premature mortality in the population with BD [6]. Several factors are involved as a reason of obesity in populations with BD, the most important seem the chaotic eating patterns or loss of control over eating, neuroendocrine dysfunction, lack of access to primary medical care, genetic predisposition, psychotropic treatment [7-10].

In addition to an increased risk of obesity, patients with mental illness seem to seek more frequently medical or surgical treatment for obesity [11,12].

Bariatric Surgery (BS) represents a treatment option in subjects with morbid obesity who fail to maintain weight loss through behavioural programs, or in those for which the weight loss achieved through behavioural programs is insufficient to improve obesity-related comorbidities. This type of surgery achieves weight loss through a combination of restrictive (sleeve gastrectomy, laparoscopic adjustable gastric banding- LAGB) and malabsorptive (biliopancreatic diversion) and mixed (Roux en-Y Gastric Bypass - RYGB) procedures [13].

Several researches have reported that approximately 22%-56% of people seeking BS meet criteria for a mental disorder [14-17]. The most frequent psychiatric disorder is an existing depressive disorder, followed by binge eating disorder and substance abuse/dependence [18,19].

Observing the potential impact of psychopathology on the

Introduction

Obesity represents an important issue for health promotion. The World Health Organization revealed that around 1.5 billion adults were overweight (body mass index, BMI \geq 25 kg/m²) and about 500 million people were obese (BMI \geq 30 kg/m²) in 2008. In the United States (US), about 34% of people is currently obese [1].

Severe obesity is frequently associated with psychiatric conditions. In a community-based study, obesity was positively correlated with several mental disorders, especially mood disorders and anxiety disorders [2].

Dixon *et al.* [3] observed that persons with severe obesity, particularly younger women with body image issues, are at elevated risk for depression and depressed subjects had 32% more probability to be obese in 5 years [4]. Empirical observations have long proposed

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outcome of BS, the estimate of accurate prevalence rates is a priority, particularly considering findings supporting a significant impact for such psychopathology on various outcomes, including weight loss. Some bariatric programs evaluate some psychiatric disorders (i.e. Bipolar Disorder) an absolute or possible contraindication to surgery, and utilize a variety of presurgical psychological testing or screening procedures. There are no available data explaining which patients with BD do receive surgery or what factors affect obesity treatment decisions among patients with BD. The reasons for delay or denial of surgery is based on the hypothesis that patients with BD have either poor metabolic and weight loss outcomes, or worsening of psychiatric symptoms and course after surgery [20].

The role of psychological factors in the outcome of BS appears imprecise. Some studies have revealed that people with psychiatric disorders have less bodyweight loss [21], but others have found no relationship or even more bodyweight loss [22]. An emphasis on psychological impact in the postoperative follow-up and investigation of possible psychological needs or need of support throughout the treatment course are important [23].

Another basic aspect for patients with mood disorders is related to the changes of the medication metabolism after surgery. Patients may present challenges after gastric bypass, due to alterations in the bioavailability and pharmacokinetics of orally administered medications. Oral drug absorption is often impaired and larger doses, intravenous, or sublingual delivery may become necessary; significant interpatient variability was observed [24]. Over time after surgery changes in the percentage of adipose tissue or in the serum protein binding can cause changes in the distribution of lipid-soluble medications or in the protein binding of medications that, therefore, may need an alteration in dosing [25]. Psychotropic drugs, including antidepressants medications are prescribed for their efficacy on the psychological wellbeing of patients, but the lack of a direct correlation of blood levels of antidepressants and a corresponding clinical effect can present a challenge both preoperatively and post operatively [26]. This is an important aspect to consider when subjects are candidate to surgery.

The purposes of this review are to evaluate:

- The types of MD and their frequency, before BS.
- The effect of BS on MD in terms of frequency and severity
- If any of the MD is considered a contraindication to surgery.
- Influence of MD on the outcomes of BS in terms of weight loss.
- Effects of BS on the metabolism of psychotropic drugs.

Material and Methods

The literature search included papers written in English that reported data on mood disorders in samples of individuals candidates to BS or in sample of patients that have been already operated. The reviewed studies were obtained by searching the database of PubMed using the search words ‘depression’, ‘bipolar disorder’, ‘mood disorders’ and ‘antidepressive drugs’ combined with ‘bariatric surgery’ and ‘obesity surgery’. In addition, a similar search was conducted for review articles published on this topic in the same period. Additional papers were obtained from reference lists in the publications found in the initial search.

Study inclusion criteria

For this review, included articles have as the main purpose to assess affective disorders in individuals undergoing or underwent to BS. Papers were included on the basis of (1) year of publication: studies were included if published between 2000 and May 2015; (2) psychiatric disorder focus: patients only with depressive or bipolar disorders; (3) empirical: papers had to provide empirical data and not just to review previous studies; (4) published: papers had to be published in peer-reviewed journals; (5) age: individuals between 18 and 65 years old; (6) type of operation: restrictive or malabsorptive BS.

Furthermore, the majority of papers obtained during the literature search focused on adults with major depressive disorder or bipolar disorder (DSM IV-V). No restrictions were placed on ethnicity or gender. Therefore, using the above criteria, 43 papers were identified for inclusion in the review, while 30 papers were excluded due to the established criteria (criteria 2: n 14; criteria 3: n 10; criteria 5: n 2 and criteria 6: n 4).

Data extraction

The following information were extracted from each study to ensure that the inclusion criteria were met and to aid the quality rating process described below: sample demographics, mood disorder diagnosis, type of sample, type of surgery and treatment, results and conclusions.

Results

Forty-three studies met inclusion criteria and are summarized in table 1, table 2, table 3, and table 4. Of 43 studies, 12 were retrospective, 3 were case reports and 28 were observational-prospective studies.

Study characteristics

The mean age of participants ranged from 28 [26] to 59.4 years [27]. Sample sizes varied from 10 [28] to 6235 [29] participants. The majority of the studies included males and females in the statistical analysis, two included only males and eight included only females.

Seventeen studies assessed the prevalence of affective disorders before surgery, 13 the prevalence and the outcome after BS, 9 evaluated the effects of the mood disorder on weight loss outcome, 4 the effect of the surgery on the treatment of the psychiatric disorders. Twenty-two studies considered different types of BS, 15 included only RYGB, 5 only LAGB and 1 only sleeve gastrectomy.

Prevalence of affective disorders in patients seeking bariatric surgery

Seventeen studies evaluated the prevalence of affective disorders in patients seeking BS (Table 1). The lifetime prevalence of mood disorders in these samples ranged between about 15% [14,30] and 50.7% [17] for depressive disorder and 5.8% [31] and 35.6% [32] for bipolar disorder, respectively. The current prevalence of mood disorder in patients seeking BS ranged between 3.4% [14] and about 60% [33] for depressive disorder and 1.4% [15] and 35.6% [32] for bipolar disorder.

De Silva *et al.*, [34] found that 33% of patients had bipolar disorders and 29% had a lifetime depressive disorder. Without a standardized evaluation, 48% of patients with a bipolar disorder had received a major depressive disorder diagnosis and 60% of subjects with major depressive disorder had not considered to have any mood disorder.

On the other side, Salwen *et al.* [30] found a lower prevalence of depressive disorders, only 15% of bariatric patients showed the presence of depressive symptoms and Grothe *et al.* [31] reported that only 5.8% of patients screened positive for bipolar symptoms, 32 of these 54 patients were given a bipolar spectrum diagnosis at clinical interview. Alciati *et al.* [12] showed high rates of affective disorder: 89% of subjects with severe obesity received a diagnosis of bipolar spectrum disorder. According to the classification made by Angst [35], one patient (1.2%) was bipolar I, 35 subjects (42.2%) were bipolar II, 21 patients (25.3%) had a minor bipolar disorder, and 17 (20.5%) had pure hypomania.

Other researchers showed intermediate rates. Hayden *et al.* [36] estimated that 39.7% of patients had Axis I diagnosis, where mood disorders had a prevalence of 26.5%. Lin *et al.* [37] revealed that 42% of the patients had at least one psychiatric disorder. The most prevalent psychiatric disorders were dysthymic disorder (20.5%), general anxiety disorder (17.2%), binge eating disorder (7.6%), major depressive disorder (7.2%). Women had more mood and eating disorders than men, but sexual differences in anxiety disorders were not found.

Table 1: Prevalence of affective disorders before surgery.

Author and Publication year	Country	Study features	N Participants	Mean age	Sex	Other features of the study	Surgery/ Setting	Instruments	Results
Da Silva <i>et al.</i> 2015 [34]	Marseille (France)	Retrospective study	92	/	/	Focusing on lifetime mood disorders prevalence	Candidates to surgery	Standardized evaluation of psychiatric comorbidity	Lifetime mood disorders prevalence: 33 % bipolar disorder, 29 % depressive disorder. 48 % of patients suffering from bipolar disorder were previously diagnosed as suffering from major depressive disorder. 60 % of the patients suffering from major depressive disorder were not considered to have any mood disorder.
Grothe KB <i>et al.</i> 2014 [31]	Rochester (MN-USA)	Retrospective study	935	47.4 ± 12.3 years	75% F	Bipolar disorder prevalence	Candidates to surgery	Mood Disorder Questionnaire (MDQ); BDI-II	5.8% of the preoperative sample screened positive for symptoms of BD, 22% of BD patients underwent bariatric surgery.
Duarte-Guerra LS <i>et al.</i> , 2014 [32]	Sao Paulo, Brazil	Retrospective study	393	43	79.1% F	To replicate previous findings on frequency of psychiatric disorders and associated factors among obese patients seeking bariatric surgery	Candidates to surgery	SCID-I	Current anxiety disorders 46.3%; lifetime psychiatric disorders 80.9%; lifetime affective disorders 64.9%, bipolar disorders 35.6%, depressive disorders 29.3%.
Salwen JK <i>et al.</i> , 2014 [30]	New York	Retrospective study	187			Childhood abuse and adult interpersonal abuse prevalence	Candidates to surgery		61% childhood abuse, 30.5% adult interpersonal abuse, 15% depressive symptoms.
Hayden MJ <i>et al.</i> , 2014 [36]	Australia	Prospective observational study	204			To evaluate the comorbidity Axis I; follow up study (2 years),	LAGB		39.7% Axis I, Mood disorders 26.5%, Anxiety disorders 15.2%, BED 13.2%. After surgery: Axis I 20%.
Lin HY <i>et al.</i> , 2013 [37]	Taiwan	Retrospective study	841		M/F	Patients 2007-2010	Bariatric surgery vs Non-surgical	Taiwanese Depression Questionnaire (TDQ); Chinese Health Questionnaire (CHQ), SCID	42% mental disorders, mood disorders 27% in surgical group.
Mitchell <i>et al.</i> , 2012 [103]	Pittsburgh (USA)	Retrospective study	199	46	M/F	Current and lifetime Axis I disorders	LAGB, RYGB	Longitudinal Assessment of bariatric Surgery	MDD lifetime 38.7%, MDD current 7%.
Hayden MJ <i>et al.</i> , 2012 [33]	Melbourne (Australia)	Observational study	201			Evaluate BDI validity in obese patients	Candidates to surgery	SCID-I, BDI-I, BDI IA	26.9% (54) Mood Disorders, 37 MDD.
Alciati A. <i>et al.</i> 2011 [105]	Milan (Italy)	Retrospective study	120	44.4 ± 10.7 (bipolar spectrum); 41.6 ± 10.9 (no psychiatric disorders)	17m/55 F (bipolar spectrum)	To evaluate the rate of childhood parental loss and relation with bipolar spectrum	Candidates to surgery	SCID-CV semi-structured interview related to childhood parental loss	91.7% had a bipolar spectrum disorder; 28% reported a childhood parental loss, more frequent in BD II.
Abiles V <i>et al.</i> 2010 [106]	Granada (Spain)	Observational study	50 patients (26 type III Obesity, 24 type IV Obesity) and 25 normal-weight controls	O-IV 38.54; O-III 39.31; CN 40.72	M/F	To analyze the psychopathological characteristics of obese candidates for bariatric surgery	Candidates to surgery	General Health Questionnaire, Rosenberg Self-Esteem Scale, Apgar Family Function Questionnaire, Spanish version of the Quality of Life Index, Eysenck Personality Questionnaire-Revised, Food Craving Questionnaire-Trait, Eating Disorders Examination-Questionnaire Version-4	The depression score significantly differed among groups, with the O-III and O-IV groups showing the highest values.

Muhlans <i>et al.</i> 2009 [17]	Erlangen (Germany)	Observational study	145	38.6 for F; 39.1 for M	M/F (146)	To investigate the prevalence of Axis I psychopathology in bariatric surgery candidates	Candidates to surgery	Structured Clinical Interview for DSM-IV (SCID); Eating Disorder Examination (EDE)	Lifetime MDD 50.7%, current MDD 25.3%.
Mauri <i>et al.</i> 2008 [16]	Pisa (Italy)	Observational study	282		M/F	Prevalence Axis I-II and QoL	Candidates to surgery	SCID I-II, Ham-D Bulimic Investigatory Test, short-form Quality of Life Enjoyment and Satisfaction Questionnaire	Lifetime Axis I 37.6%; Mood Disorders lifetime 22.0%, current MDD 4.5%. QoL significantly more impaired in patients with comorbid Axis I.
Wildes JE <i>et al.</i> , 2008 [107]	Pittsburgh (USA)	Retrospective study	230			Childhood maltreatment and Axis I diagnosis	Candidates to surgery	Childhood Trauma Questionnaire, short form; SCID-I	66% history of childhood maltreatment; elevated rates of both unipolar and bipolar mood disorders.
Kalarchian <i>et al.</i> 2007 [15]		Observational study	288			Prevalence psychiatric disorders	Candidates to surgery		Lifetime psychiatric disorders (66.3%); Bipolar Disorder 1.4%.
Alciati <i>et al.</i> 2007 [12]	Milan (Italy)	Retrospective study	83	44.4 ± 10.7	M/F	To investigate the prevalence of bipolar spectrum (including subsyndromal hypomania) in patients seeking surgical treatment).	Candidates to surgery	SCID-CV questionnaire; Hypomania Symptom Check list (HCL-32)	Bipolar spectrum disorder 89% of the sample, highest prevalence BD -II, comorbidity with panic disorder 30%.
Rosenburger PH <i>et al.</i> , 2006 [14]	New Haven (USA)	Retrospective study	174			Current and lifetime psychiatric disorders and association with eating disorders	Candidates to surgery	SCID-I	MDD 14.9% (Lifetime), 3.4% (Current).
Sanchez-Román S. <i>et al.</i> , 2003 [27]	Mexico	Retrospective study	70	49 +/-10.4	25 M, 35 F		Candidates to surgery	SCID-I	60% Axis I disorder, most frequent anxiety disorders and mood disorders.

F: Female; M: Male; RYGB: Roux-Y-Gastric Bypass; LAGB: Laparoscopic Adjustable Gastric Banding; MDD: Major Depressive Disorder; BD: Bipolar Disorder; BED: Binge Eating Disorder; SCID-I: Structured Clinical Interview for DSM IV Axis I disorders; Ham-D: Hamilton Rating Scale for Depression; BDI: Beck Depression Inventory; Beck Depression Inventory-II (BDI-II); QoL: Quality of Life

Prevalence of affective disorders post-surgery

Thirteen studies investigated the prevalence and the outcome of affective disorders after surgery (Table 2). De Zwaan *et al.*, [38] found that the point prevalence of depressive disorders but not of anxiety disorders decreased after surgery. The presence of depression before surgery constituted a predictor of the persistence of the depressive disorder after surgery and a lower degree of weight loss at 24-36 months follow up [38]. Other studies have confirmed a reduction of depressive disorders after surgery [39-44] and a reduction of antidepressant prescriptions [29].

The improvement of depressive symptoms was reported both in patients underwent to LAGB [40-42] and underwent to RYGB [29,43].

On the contrary, other studies showed an increase of depressive symptoms after surgery [3,45,46]. Ivezaj *et al.* [45] observed that from baseline to 6 months postsurgery no subjects had a discernible worsening in mood, 3.7 % reported discernible worsening in mood from pre surgery to 12 months postsurgery, and 13.1 % reported observable worsening in mood from 6 to 12 months postsurgery. Thus, the majority of patients with discernible worsening in mood experienced these mood changes between 6 and 12 months postsurgery or in the following year [46].

Observing the course of bipolar disorder after surgery, Nepal *et al.*, [47] reported the case of a new onset of mania and Kaltsounis *et al.* [26] described in a schizoaffective patient a reactivation of a manic state following the operation.

On the opposite, Amhed *et al.* [48] found that among 144 patients with BD who underwent BS compared with 1,440 matched unexposed patients followed for around 2 years, the BS group was not associated with significant differences in the risk of psychiatric hospitalization or change in rate of outpatient visits for psychiatric services.

Effects of affective disorders on weight loss outcome

Nine studies investigated the influence of psychopathology on weight loss outcome after BS (Table 3). Some studies have found poor weight loss postoperatively in the presence of preoperative mood disorders [22,49,50]. In 2008, Kalarchian *et al.* [51] provided that the presence of a lifetime Axis I disorder, especially mood or anxiety disorders, was associated with poorer weight outcomes up to six months after surgery. However, current Axis I disorders and Axis II personality disorders were not related to outcomes at six months.

Legenbauer *et al.* [52] showed that in patients underwent to BS, depression was not associated with weight changes at the 1-year follow-up, but after 4 years depression (current and lifetime) represented a predictor of a smaller body mass index loss.

De Zwaan *et al.* evaluated the prognostic significance of preoperative and postoperative anxiety and depressive disorders and they reported that patients with both depressive and anxiety disorders at baseline (current and lifetime) lost significantly less weight after surgery. Postoperative depressive disorder was negatively related with weight loss at the 24-36 month follow-up assessment point [38].

Otherwise, Averbukh *et al.* [22] reported that weight loss at 1 year was significantly associated to the BDI score before surgery. BDI score was also found to significantly predict the amount of weight lost 1 year after surgery, where more depressed individuals tended to lose greater amounts of weight compared with less depressed individuals.

Moreover, other studies that did not provide any relationship between the presence or absence of preoperative psychiatric disturbances and weight loss after surgery [53-55]. Thonney *et al.* sustained that psychological outcomes and eating disorders did not predict weight loss 2 years after gastric bypass [45,56].

Table 2: Prevalence of affective disorders after surgery.

Author and Publication year	Country	Study features	N Participants	Mean age	Sex	Other features of the study	Surgery/ setting	Instruments	Results
Ivezaj V & Grilo Cm 2015 [45]	New Haven (CT-USA)	Prospective, longitudinal study	107		94 F; 13M	To evaluate the frequency of bariatric patients who experienced discernible increases in depression levels following surgery and explored their correlates. 6- 12-months follow up	RYGB	BDI; Eating Disorder Examination EDE-Q; Self-esteem (RSES), Social functioning (SF-36)	14 (13.1 %) participants reported discernible increases (BDI-Increase), 14 (13.1 %) reported discernible decreases (BDI-Decrease), and 79 (73.8 %) did not report discernible changes (no change) in BDI scores from 6 to 12 months postsurgery. By 12 months postsurgery, the BDI-Increase group had significantly higher depression scores.
Nepal H et al. 2015 [47]	Springfield (IL-USA)	Case report	1	57	F	One of complications after bariatric surgery is represented by neuropsychiatric disorders and psycho-behavioral symptoms. Onset 2 months after surgery.	RYGB	Psychiatric evaluation, clinical interview	Primary mania.
Ahmed AT et al. 2013 [60]	San Francisco (USA)	Prospective, longitudinal study	144 patients with bipolar disorder who underwent BS and 1440 controls	43.9+/-10	88.9% F, 11.1%M	To determine if bariatric surgery alters psychiatric course among stable patients with bipolar disorder	Bariatric surgery	Psychiatric hospitalization: defined as any inpatient stay at a psychiatric hospital.	9% BS and 10.6% unexposed to surgery had psychiatric hospitalization during follow-up.
Cunningham JL et al. 2012 [46]		Retrospective study	439			Antidepressant usage after surgery	RYGB		23% increase antidepressant, 40% same antidepressant, 18% change, 16% decrease or discontinued antidepressant.
de Zwaan et al. 2011 [38]	Nuremberg, Germany	Prospective, longitudinal study	107	37.5 +/- 9.7	32 M; 75 F	Assessment after 6-12 months and 24-36 months.	Bariatric surgery	SCID -I	The point prevalence of depressive disorders but not of anxiety disorders decreased significantly after surgery. Patients with both depressive and anxiety disorders at baseline (current and lifetime) lost significantly less weight after surgery. Postoperative depressive disorder was negatively associated with weight loss at the 24–36 month follow-up assessment point.
Hayden et al. 2011 [40]	Victoria, Australia	Prospective, longitudinal study	191	41+/-9		Assessment at baseline and after 12 months	LAGB	BDI	Patient scores on the negative self-attitude subscale were significantly greater than the two other subscales and showed the greatest improvement 1 year following LAGB.
Sultan et al. 2009 [41]	New York	Prospective, longitudinal study	53	46.9		BMI lower than 35, follow up 2 years. Study parameters included preoperative age, gender, BMI, presence of comorbidities, percentage of excess weight loss (%EWL), and resolution of comorbidities.	LAGB		Substantial improvement occurred for the following comorbidities evaluated: hypertension, depression, diabetes, asthma, hypertriglyceridemia, obstructive sleep apnea, hypercholesterolemia, and osteoarthritis.
Segal JB et al. 2009 [29]	Baltimore (USA)	Retrospective study	6235	44	M/ F (F = 82%)	To compare the mean number of medications at the time of surgery and in the subsequent year	RYGB, Gastroduodenostomy		Decrease in the mean number of prescriptions filled for antidepressant medications, with a 9% decrease by 12-months.
Schowalter et al. 2008 [42]	Wuerzburg, Germany	Prospective, longitudinal study	248			128 patients were treated with gastric banding and 120 controls	LAGB	BDI	In the preoperative assessment, 35% of all obese patients suffered from clinically relevant depressive symptoms. After 5 to 7 years, patients with gastric banding improved significantly in depression, whereas no change was found in patients without gastric banding.

Burgmer <i>et al.</i> , 2007 [39]	Dortmund, Germany	Prospective, longitudinal study	149	38.8 ± 10.3	47 M; 102 F	To evaluate depressive symptoms, self-esteem and health-related quality of life 2 years after bariatric surgery.	Gastric restrictive surgery		Pre-surgery, 40.5% (n=62) of the patients suffered from depressive symptoms of clinical relevance. These depressive symptoms persisted in 17.7% (n = 27) 1 year and in 16.4% (n = 25) 2 years after surgery.
Emery <i>et al.</i> 2007 [43]	Columbus (USA)	Prospective, longitudinal study	13	46.9 ± 5.7	F	To examine the relationship of inflammation and depression among gastric bypass patients in a 12-month longitudinal study.	RYGB	Self-report measures of depression	Significant reductions in BMI, participants experienced significant reductions in C-reactive protein (CRP), IL-6, and depressive symptoms. Decreased depression during the 12-month follow-up was highly correlated with reduced CRP.
Dixon <i>et al.</i> 2003 [3]	Melbourne, Australia	Prospective, longitudinal study	487	41.2 ± 9.7	M (15%)/ F	To examine depression before and after surgically induced weight loss.	LAGB	BDI	Weight loss was associated with a significant and sustained fall in BDI scores, with a mean +/- SD score of 7.8 +/- 6.5 at 1 year and 9.6 +/- 7.7 at 4 years after surgery. Greater falls in BDI score at 1 year were seen in women, younger subjects, and those with greater excess weight loss.
Kaltsounis <i>et al.</i> 2000 [26]		Case report	1	27	M	To report the use of intra- venous valproate sodium for the treatment of severe manic symptoms that developed after gastric bypass surgery	RYGB	Monitoring during hospitalization; C linician-Administered Rating Scale for Mania (CARS-M)	Intravenous valproate was initiated conservatively at approximately 4 mg/ kg every 60 minutes. Intravenous administration of valproate seemed to be efficacious, well tolerated, and pharmacokinetically appropriate.

F: Female; M: Male; BS: Bariatric Surgery; BMI: Body mass Index; RYGB: Roux-Y-Gastric Bypass; LAGB: Laparoscopic Adjustable Gastric Banding; MDD: Major Depressive Disorder; BD: Bipolar Disorder; SCID-I: Structured Clinical Interview for DSM IV Axis I disorders; BDI: Beck Depression Inventory; Beck Depression Inventory-II (BDI-II)

Effects of the surgery on drug metabolism

Four studies investigated the change of drugs bioavailability after surgery. One of these showed that in Roux-en-Y gastric bypass patients treated with a dose of 100 mg sertraline for major depression, the mean concentration/time curve (AUC) was lower than in non-surgical comparison subjects [28] (Table 4).

Roerig *et al.*, [57] analyzed the alteration of the AUC of the antidepressant duloxetine, after the RYGB procedure. The mean AUC was significantly reduced for the BS group compared to the nonsurgical control group. The T_{max} was also significantly shorter for the BS group (2.2 hours) compared to the nonsurgical control group (6 hours).

Hamad *et al.* [58] performed a study in which longitudinal Serotonin Reuptake Inhibitors (SRI) pharmacokinetic analysis was collected for 1 year following BS. In eight of the 12 patients, 1 month after gastric bypass the AUC values decreased to an average of 54% of preoperative levels (range = 36%-80%); in six of these patients, after 6 months, AUC values returned to baseline levels (or greater). Although a significant reduction in AUC was observed for the entire sample, it was more evident in the selective serotonin reuptake inhibitors (SSRIs) group than the serotonin-norepinephrine reuptake inhibitors (SNRIs) group [58].

Discussion

The literature reviewed shows a heterogeneous literature about prevalence of psychopathology among subjects with obesity seeking BS. Several studies showed a high diffusion of mood disorders, while other found a low prevalence [18, 27,59-62]. Even if the exact

diffusion of mood disorders among bariatric patients is still unclear, individuals seeking medical treatment for obesity (including either surgery or pharmacotherapy) are more likely to have a positive anamnesis for depression and anxiety than obese individuals seeking programs based only on dietary restriction or promote weight control [63]. The association of obesity and depression has been extensively supported and at the present obesity is considered to increase the risk of depression and depression seems to be predictive of developing obesity [62]. These relations can be explained considering both biological and psychological mechanisms. Inflammation as well as HPA-axis dysregulation typically found in obesity are thought to be mediators of the associations.

Furthermore, considering that obesity is often accompanied by various physical illnesses, such as diabetes, cardiovascular disease and obstructive sleep apnea and that these comorbid conditions are also associated with psychiatric disorders, such as depression [64,65], it is possible to understand that, for several reasons, BS candidates present high rates of psychopathology. Moreover, another important aspect is that in community samples, psychiatric disorders and in particular BD are frequently underdiagnosed and confused with major depressive disorders [66,67]. This seems especially evident in patients with obesity because major depressive episodes appear predictive of bipolar disorder in this specific population [68]. Consequently, a high proportion of psychiatric disorders may be underdiagnosed in obese patients and these frequent misdiagnoses may severely influence psychiatric and medical prognosis, above all for the inadequate or insufficient treatment [34].

Patients with bipolar symptoms disorder show more psychopathology as higher depression severity and generalized anxiety, higher rates of childhood trauma and emotional eating and

Table 3: Effects of psychiatric disorders on weight loss outcome.

Author and Publication year	Country	Study features	N Participants	Mean age	Sex	Other features of the study	Surgery/ setting	Instruments	Results
White <i>et al.</i> 2015 [44]	New Haven, USA	Prospective, longitudinal study	357			To examine the prognostic significance of depressive symptoms in bariatric surgery patients over 6-12- 24-months of follow up.	RYGB	Beck Depression Inventory	Depressive symptoms characterized 45 % of patients prior to surgery, and 12 % at 6-month follow-up, 13 % at 12-month follow-up, and 18 % at 24-month follow-up. Preoperative depressive symptoms did not predict postoperative weight outcomes. Postsurgery depressive symptoms were predictive of weight loss outcomes.
Steinmann WC <i>et al.</i> 2011 [92]	Columbia USA	Retrospective study				Comparison of patient underwent to RYGB: bipolar disorder group, other psychiatric conditions group, without psychiatric diagnosis group	RYGB	Evaluation of the differences in demographics, physical comorbidities, and psychological conditions before surgery and behavioural noncompliance after surgery.	At 1 year, overall mean percent weight loss exceeded 35%, and mean BMI was 32. These outcomes were remarkably similar and not significantly different for those with bipolar disorder, other psychological conditions, and those without.
Legenbauer <i>et al.</i> 2011 [103]	Bochum, Germany	Prospective, longitudinal study	153	38.8%	66.9% F	Lifetime diagnosis of a mental disorder was defined as presence of a mental disorder only in the past. Body weight was measured at baseline, 1 year after baseline, and 4 years after baseline.	Bariatric surgery	Munich-CIDI to assess current and lifetime depressive disorders including major depression and dysthymia	Depression was not associated with weight changes at the 1-year follow-up. After 4 years: depression (current and lifetime) predicted smaller body mass index loss, whereas lifetime diagnosis of eating disorder was associated with greater weight loss.
Semanschin-Doerr DA <i>et al.</i> 2010 [50]	Cleveland, USA	Prospective, longitudinal study	104		78.6% white, 71.2% F	43.1% had a current, and 62.5% a lifetime, diagnosis of a mood disorder. 1-Year follow-up	Sleeve gastrectomy		Patients with current or lifetime mood disorders had a significantly lower %EWL. After removing patients with bipolar disorder from the analyses, no significant differences were found in the %EWL between patients with and without a lifetime history of depressive disorders.
Thonney <i>et al.</i> 2010 [56]	Geneva, Switzerland	Prospective, longitudinal study	43	39.3 ± 1.4	F	2 years follow up	RYGB	BDI; Hospital Anxiety and Depression Scale	Decreases in depression, anxiety (P <.05), and eating disorder scores were measured 2 years after surgery. Both excess weight loss and change in body mass index were associated with improvements in all measured psychological outcomes 2 years after surgery.
Coleman <i>et al.</i> 2010 [55]	Pasadena (USA)	Prospective, longitudinal study	110	43,5	F	1-year follow up	RYGB	Evaluation of the differences in demographics, physical comorbidities, and psychological conditions before surgery and behavioural noncompliance after surgery.	The only differences between patients with successful and unsuccessful weight loss were found for sleep apnea before surgery, exercise noncompliance in the second year after surgery, and dumping syndrome in the first 6 months after surgery.
Legenbauer <i>et al.</i> 2009 [49]	Dortmund,- Germany	Prospective, longitudinal study	531 (151 BS)	38.8 ± 10.3	66.9 % F in BS group, white	To investigate the impact of current mental disorders on weight loss: 4-year follow-up	Comparison participants in a conventional treatment, obesity surgery patient, obese control individuals		Patients with a depressive and/or anxiety disorder lost significantly less weight compared with those without a comorbid mental diagnosis. Binge eating behaviour at baseline did not predict weight loss at 4-year followup.

Kalarchian <i>et al.</i> 2008 [69]	Pittsburgh, USA	Prospective, longitudinal study	207 (97.2% white)	45.8 ± 9.5	83.1% F; 16.9% M	6-month follow up	RYGB	SCID-I	Lifetime mood disorder was associated with a smaller decrease in BMI.
Averbukh Y <i>et al.</i> , 2003 [22]	New York	Prospective, longitudinal study	145			to evaluate the association between pre-surgical severity of depression and success at weight loss following Roux-Y gastric bypass (RYGBP)	RYGB	BDI	Weight loss at 1 year was significantly related to the BDI score before surgery. BDI score was also found to be a significant predictor of the amount of weight lost (kg) 1 year after surgery.

F: Female; M: Male; BS: Bariatric Surgery; BMI: Body mass Index; RYGB: Roux-Y-Gastric Bypass; LAGB: Laparoscopic Adjustable Gastric Banding; MDD: Major Depressive Disorder; BD: Bipolar Disorder; BED: Binge Eating Disorder; SCID-I: Structured Clinical Interview for DSM IV Axis I disorders; Ham-D: Hamilton Rating Scale for Depression; BDI: Beck Depression Inventory; Beck Depression Inventory-II (BDI-II); QoL: Quality of Life

Table 4: Psychopharmacological treatment after surgery.

Author and Publication year	Country	Study features	N Participants	Mean age	Sex	Other features of the study	Surgery/ setting	Instruments	Results
Roerig <i>et al.</i> 2013 [57]	Fargo, USA	Observational study	10 patients, 10 controls			To determine to what extent the RYGB procedure alters the area under the plasma concentration/ time curve (AUC) of the antidepressant, duloxetine (60 mg/die): 1 year post-RYGB	RYGB	Nineteen plasma samples were obtained during 72 hours to characterize the plasma level profile.	The bariatric surgery group was exposed to only 57.7% of duloxetine as compared to the nonsurgery group.
Roerig <i>et al.</i> 2012 [28]	Fargo, USA	Observational study	5 patients, 5 controls			To determine to what extent RYGB alters the area under the plasma concentration/time curve (AUC(0-10.5)) of the antidepressant, sertraline (100 mg /die).	RYGB	Plasma samples were obtained for 10.5 hours.	The mean AUC(0-10.5) and the maximal plasma concentration were significantly smaller for the postbariatric surgery group (compared with the nonsurgical control group).
Hamad GG <i>et al.</i> 2012 [58]	Pittsburgh, USA	Prospective, longitudinal study, 6- 12-months follow up	12	41.9	11 F, 1 M	Timed blood samples for SRI plasma levels were drawn for pharmacokinetic studies before surgery and 1, 6, and 12 months afterward. Maximum concentration, time to maximum concentration, and area under the concentration/time curve (AUC) were determined.	RYGB	SCID-IV; Structured Interview Guide for the Hamilton Depression Rating Scale–Atypical Depression Symptom Version (SIGH-ADS)	AUC values 1 month after surgery dropped to an average of 54% of preoperative levels; in 6 of these patients, AUC values returned to baseline levels (or greater) by 6 months. 4 patients had an exacerbation of depressive symptoms, which resolved by 12 months in three of them. 3 of the four patients had a reduced AUC level at 1 month and either gained weight or failed to lose weight between 6 and 12 months.
Tripp AC <i>et al.</i> , 2011 [101]	Pittsburgh, USA	Case report	1	51	M	Treatment with Lithium at therapeutic dose	RYGB		Alterations in drug dissolution and absorption as result of RYGB

F: Female; M: Male; BS: Bariatric Surgery; BMI: Body mass Index; RYGB: Roux-Y-Gastric Bypass; LAGB: Laparoscopic Adjustable Gastric Banding; MDD: Major Depressive Disorder; BD: Bipolar Disorder; BED: Binge Eating Disorder; SCID-I: Structured Clinical Interview for DSM IV Axis I disorders; Ham-D: Hamilton Rating Scale for Depression; BDI: Beck Depression Inventory; Beck Depression Inventory-II (BDI-II); QoL: Quality of Life

a lower capacity to with stand negative emotional states, than patients without bipolar symptoms [31]. Patients with bipolar symptoms describe more alcohol misuse, as would be expected given the comorbidity of substance use and bipolar symptoms [69]. Given the comorbidity of the two disorders, substance abuse is a risk for patients with bipolar illness who may be exposed to an increased vulnerability for addiction postoperatively.

Medication-associated weight gain is the most commonly reported side effects among patients with BD and it is an additional factor that reduces the quality of life. In addition to an increased risk for obesity, patients with BD have an insufficient obesity treatment [70] and may be denied surgical treatment due to their psychiatric diagnosis. As said, patients with BD seem to have either poor metabolic and weight loss outcomes, or worsening of psychiatric symptoms and course after surgery [20]. This situation was confirmed by Grothe *et al.* [31], patients with bipolar symptoms were denied BS after the first visit for psychiatric reasons and one of four of these patients had a psychiatric hospitalization within the year after evaluation, which could have diverted their pursuit of BS. Considering these findings, the presence of bipolar symptoms seems a negative predictor of adherence to a structured program [31].

The researches about prevalence of mood disorders after surgery appear equally inconclusive. In several cases the studies report a reduction of depressive or bipolar symptoms, but in other cases the diffusion remains similar [71]. Several factors might explain change in psychiatric functioning after BS. One of plausible mechanisms through which successful treatment of obesity would improve psychiatric course among patients with MDD and BD, is that weight loss is generally associated with decreased depressive symptoms and improved quality of life [60,62,72,73]. Moreover, the deactivation of inflammatory pathways, normalization of HPA axis functioning, reversal of insulin resistance could be pathways to explain the significant reduction of depressive symptoms after BS, but these possible mechanisms need to be further examined.

In other cases, subjects with a positive anamnesis for depression have shown a reactivation of depressive symptoms after surgery. Some explanations for the exacerbation involve the reduced absorption of antidepressive drugs or tryptophan, which is a precursor of serotonin [74], and the malabsorption of minerals and vitamins (iron and folate) that are enzymatic cofactors in the synthesis of neurotransmitters [75,76]. In young women, iron deficiency is associated with higher

depressive symptom scores [77]. Folate deficiency has been linked to a reduced response to antidepressants [78]. The different antidepressants and nutritive absorption can be caused by a diminished intestinal surface area available for drug absorption as a result of the Roux-en-Y gastric bypass anatomy [79].

Considering the effects of surgery on subjects with BD, although some BS centres evaluate these patients not eligible for surgery due to their psychiatric diagnosis, the study of Amhed *et al.* [48] showed that BS did not adversely influence psychiatric course among stable patients with BD, suggesting that people with stable BD can be evaluated for BS using the same criteria as other patients.

However, the complexity in the treatment of BD patients has to be considered and the possibility of a medication noncompliance and medical or surgical situations that may limit the oral intake of medication [26], as a prolongation of an agitated state, should be monitored. In addition, BS might increase depressive or manic symptoms caused by postoperative vomiting or malabsorption of medications [80]. A reduced absorption of mood stabilizers or antipsychotics can cause an insufficient protection from relapses (manic or depressive phases) [81-83].

The reported inverse relationship between severe obesity and substance use disorders in BD places the possibility that significant weight loss may be associated to an increase in use of alcohol or other drugs [84,85]. Moreover, BS is accompanied with increased risk of death by suicide, with an estimated rate of suicide post-BS of 4.1/10,000 person-years [86,87].

Considering that BD patients can find a more complicated course after surgery, they need a specific monitoring in order to detect early a reactivation of a depressive or bipolar symptoms.

Different studies reported conflicting results about the relationship between the presence of psychiatric condition and weight loss outcome [87,88].

Some authors report a negative influence of mental comorbidity, as adjustment, depressive, and anxiety disorders, on long-term weight loss [21]. This can be explained observing that patients with depressive disorders are vulnerable to affect adherence to the postoperative regimen. Depression may reduce the patient's level of energy and motivation, or modify their appetite, making them less careful about their health [37].

The possible impact of depressive disorders on eating behaviour or physical activity also, at least within the first 12 to 18 months [89,90], cannot compete with the considerable restriction after BS [3]. Moreover, vulnerability for depressive disorders might exert an influence after the so-called "honeymoon phase": after this period, some weight regain usually takes place.

It is possible that different mechanisms underlie weight loss during and shortly after treatment compared with the long-term course and for this reason, the available data regarding influence on weight loss have to be considered with caution [91].

As the depressive disorder, the bipolar disorder often is accompanied by a reduced compliance to the treatments, but in addition, higher levels of impulsivity, substances abuse and mood instability are more frequently associated. All these aspects can influence the weight loss outcome after surgery. On the contrary Steinmann *et al.*, comparing patients underwent to RYGB (bipolar disorder group, other psychiatric conditions group, without psychiatric diagnosis group), observed that the weight loss outcome at 12 months in patients with bipolar disorder was remarkably similar and not significantly different for those with or without other psychological situations [92].

Finally one important aspect to consider in patients with mood disorders underwent to BS is the bioavailability of psychiatric medications after Roux-en-Y gastric bypass. After this operation, ingested food no longer proceeds through the gastric antrum and

duodenum; consequently, nutrient and drugs absorption is modified [79,93-95].

The mechanism of the postsurgical reduction in SRI levels may be associated to the markedly reduced gastric acidity [96] and the absorption of the tablet form of SRI is reduced as a result of reduced solubility. After surgery, the cardia is disconnected from the distal stomach; therefore, most of the parietal cells are excluded from the pouch and gastric pH is increased, causing a significantly less dissolution compared with the normal environment [97]. Different drug dissolution features may explain these results. In physiologic solutions prepared to approximate a presurgical compared with a postsurgical gut environment [97], the SSRIs sertraline, fluoxetine, and paroxetine appeared significantly less soluble in the postsurgical than in the presurgical solution. No significant difference was observed between solutions for venlafaxine, which supports findings of Hamad *et al.* [58] of less dramatic reductions in the bioavailability for SNRIs compared with SSRIs. The differences between SNRIs and SSRIs may be better explained with solubility characteristics than with drug class, since solubility of the SSRI citalopram did not differ before and after BS [58].

After gastric bypass surgery, the volume of distribution might be lower because of the adipose tissue is reduced. The concentration of drug-binding α -1-acid glycoprotein (AAG) has been observed to double in patients with obesity. In weight loss after surgery, serum AAG may decrease, possibly needing dose adjustments for highly bound drugs like Tricyclic Antidepressants (TCAs) [98,99]. Frequent monitoring of the albumin level is a fundamental, especially in the first 2 years postoperatively [100]. Other involved factors can be gastric emptying, modified after gastric transection [93] and the rapid weight loss in the first 18 months that dramatically changes the volume of distribution of drugs.

Tripp *et al.*, [101] identified a case report of lithium toxicity at therapeutic doses after RYGB. His creatinine was elevated, probably secondary to dehydration, which most likely was the main cause of his lithium toxicity. However, in addition to dehydration, increased dissolution and greater absorption of lithium as a result of RYGB could have hypothetically contributed or could have been the cause of lithium toxicity. The greater dissolution of the extended release preparation in the post-bypass environment could cause an increased absorption and increased plasma peak levels [101].

Limitations

After reviewing the 43 studies, several common limitations were identified. The demographic data provided by the various authors were inadequate. The age, gender, ethnicity and socioeconomic status (SES) of participants were not provided in all studies. This lack of descriptive data limits the generalizability of the findings, as ethnicity and SES are known to be important demographic elements in subjects with obesity [102].

Another limiting factor is that there viewed studies used different study design and assessment tools with the risk to overestimate or underestimate the real prevalence of the affective disorders. The evaluation instrument used in all the studies on BS candidates was the English, Italian or the German version of the SCID Interview (SCID-I). Four studies [14,16,17,103] conducted face-to-face interviews. Moreover, some studies considered only females or males and this represents a confusing factor because females had a higher prevalence of mood disorders [37] and only few study included a control group for the analysis. Lastly, twenty-one studies grouped all participants underwent to BS together, and did not specify the type of surgery (restrictive, malabsorptive or restrictive malabsorptive). The surgical options are different not only in the mechanism of functioning (restrictive versus malabsorptive), but also in the effects in terms of weight loss [104]. These findings suggest that when subtypes of BS are combined, important outcomes may be concealed.

Future research should make efforts to overcome these limitations.

Conclusion

Among morbidly obese patients who have failed behavioural weight loss approaches, BS constitutes a potentially effective solution. Upon reviewing the most recent literature on mood disorders and BS the following are recommendations for improving the clinical and research approach:

1. Although obesity surgery is not contraindicated for several psychiatric disorders, an evaluation of preoperative psychiatric status of patients, an adequate preoperative treatment and postoperative psychological support should be provided to increase the long-term success of these operations and reduce the risk of complications.
2. The majority of the studies on patients undergone to BS has generally reported a substantial reduction of psychopathology after surgery both in the short and long follow up.
3. The lifetime presence of mood disorders after BS seems significantly to moderate the post-surgical weight loss.
4. BS shows important effects on metabolism of psychotropic drugs and for this randomized prospective pharmacokinetic studies examining medication alterations in the BS patient and the clinical significance of any alterations are fundamental.

Research into psychiatric and metabolic outcomes of BS among patients with psychiatric disorders is urgently required to head clinical decision-making and policy decisions regarding bariatric procedures in the population with similar pathologies.

Conflicts of Interest Disclosure

All authors have no conflicts of interest to disclose.

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