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Outcomes of Deep Brain Stimulation on Adolescent and Adult Women with Refractory Anorexia Nervosa

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Abstract

Background: Anorexia nervosa is a psychosomatic disease that affects many women worldwide. It is commonly associated with comorbidities and has the highest mortality rate of any mental illness. Current treatments are often insufficient in treating this disease and frequently fail to improve the health and quality of life of these women. Deep brain stimulation (DBS) is an established treatment for neurological movement disorders and is emerging as a treatment for psychological disorders similar to anorexia. Due to this similarity, DBS may be an option for treating these women who fail other treatments. This review looks at the outcomes of DBS as a treatment for anorexia nervosa.

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: deep brain stimulation, anorexia nervosa, and female. Relevant articles were assessed for quality using GRADE.

Results: Through screening, three studies were found that fit the criteria for this review. This included three observational studies. All three showed improved outcomes in the majority of subjects and demonstrated the relative safety of the procedure. Outcomes included body mass index (BMI), vital signs, anxiety, depression, obsessive-compulsion, quality of life, intelligence, memory, social functioning, brain glucose metabolism, and adverse events associated with the surgery. Though the results of the three studies were promising, the overall quality of the studies was very low. More research is needed to demonstrate the efficacy and safety of this treatment and better understand its mechanism for treating this disorder.

Conclusion: DBS may play an important role in treating anorexia nervosa that has proven refractory to standard treatments. DBS may be associated with improvement in physical symptoms, psychological outcomes, and changes in brain glucose metabolism, but more research is needed to further examine this association.

Keywords: deep brain stimulation, anorexia nervosa, female

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To *my parents*: Thank you for supporting me in everything I do. Thank you for encouraging me when things were hard and for always believing in me.

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List of Abbreviations

AN	Anorexia nervosa
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	Body mass index
CBT	Cognitive behavioral therapy
DBS	Deep brain stimulation
ED	Eating disorder
HAMD	Hamilton Depression Rating Scale
MDD	Major depressive disorder
NAc	Nucleus accumbens
OCD	Obsessive-compulsive disorder
PTSD	Post-traumatic stress disorder
SSRIs	Selective serotonin reuptake inhibitors
YBC-EDS	Yale-Brown-Cornell Eating Disorder Scale
YBOCS	Yale-Brown Obsessive-Compulsive Scale

Outcomes of Deep Brain Stimulation on Adolescent and Adult Women with Refractory Anorexia Nervosa

BACKGROUND

Anorexia nervosa (AN) affects up to 4% of women throughout the world in their lifetime.[1] As a very common psychosomatic disorder, it is associated with high morbidity and mortality, yet is poorly understood. While it is very prevalent in the United States and other Western cultures, it is growing increasingly common in non-Western countries, such as China.[2] AN is defined in the DSM-V by the following criteria: restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health; intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight; and disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight. Severity is measured by body mass index (BMI), with $\geq$17 kg/m^3 classified as mild, 16-16.99 kg/m^3 as moderate, 15-15.99 kg/m^3 as severe, and <15 kg/m^3 as extreme.[3]

Up to 24.3% of patients who have AN also suffer from a comorbidity, some of which are serious and life threatening.[1] Comorbid conditions include osteoporosis, cardiac dysfunction, neurological deficits, renal dysfunction, other psychosomatic disorders, and suicide. This disorder along with its complications account for many office visits and hospitalizations, with Lipsman et al[4] reporting a near combined 50 years of hospitalizations between its six subjects. With a mortality rate approaching 20%, it is the most deadly of all the psychosomatic disorders.

While there are multiple methods currently used for the treatment of AN, many of them are deemed ineffective in a large percentage of patients. Conventional treatment efforts include pharmacotherapy and psychotherapy. Common medications used include SSRIs as first line therapy along with psychopharmaceuticals and the off-label use of neuroleptics such as olanzapine. However, these medications have been shown to have a weak effect at best.[5] Psychotherapy and self-help programs, such as family therapy and cognitive behavioral therapy, seem to be the most effective treatments for AN at this time.[6-8] However, studies[9-11] report that 30% of AN patients that undergo these conventional treatments report little, if any, success while a mere 33% report full recovery. In addition, it has been shown that treatment by weight gain alone results in a faster relapse than if comorbid mood and anxiety symptoms are targeted.[12-16]

Brain regions have been studied and corresponding glucose metabolism has been measured in order to determine patterns among women with AN. Patterns of increased or decreased metabolism have been observed in certain brain regions in subjects with psychological disorders. Similar patterns have been found in the subcallosal cingulate region in patients with AN as in patients with these other disorders (e.g., depression and anxiety).[17-21] Examining and targeting these specific locations will be critical in designing DBS treatment for these patients.

Furthermore, hypermetabolism of glucose has been noted across patients with AN in many areas, including the caudate nuclei, lateral inferior frontal cortex, thalamus and putamen.[22] In contrast, hypometabolism has been consistently noted in the parietal lobe. The frontal cortex has been associated with punishing stimuli[23] and compulsive behaviors.[24] The parietal cortex is the most consistently involved area in AN and may play a part in mood regulation[25] and proprioception and visual information of one's own body, possibly leading to altered self-

perception of body image.[26] The nucleus accumbens has been associated with the rewarding nature of the disorder and the physiological drive to eat.[27] The lentiform nucleus has been connected to altered reward and affect, decision making, and executive control along with the stereotypic motor movements and decreased food ingestion associated with the disorder.[28] The subcallosal cingulate has been connected to a negative affect due to decreased serotonin binding.[18,19,29,30] The hippocampus and amygdala have been associated with the intense fear of weight gain, fearful emotional processing of negative words concerning body image,[31] and their own fat image.[32] Lastly, the insula is also associated with body image perception[33] and altered interoceptive processing[34], which could be associated with lack of recognition of the symptoms of malnutrition and diminished motivation to change.[35]

Deep brain stimulation has been used for over 25 years[4] and is an acceptable treatment for neurological movement disorders, such as Parkinson disease and essential tremor. Recent studies have shown that it may also be helpful in those with neuropsychiatric disorders, such as severe depression, obsessive-compulsive disorder, and other mood and anxiety disorders.[36,37] Due to similarities in these psychological disorders to AN, it is possible that DBS could offer an effective treatment for this often under-treated disorder. This systematic review looks at the research done in this area to evaluate its potential effectiveness and safety.

METHODS

An exhaustive search of the medical literature was performed using Medline-OVID, CINAHL, and Web of Science. The following keywords were used: anorexia nervosa, deep brain stimulation, and female. Inclusion criteria included studies performed on women with a diagnosis of anorexia nervosa that had proven refractory to conventional treatment (including

pharmacotherapy, psychotherapy, hospital admissions, etc.). Exclusion criteria included studies in a language other than English, studies in which DBS was performed for a primary reason other than anorexia nervosa, or studies performed on subjects other than humans. Reviews and magazine articles were also excluded. Articles were evaluated for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[38] and are included in this systematic review.

RESULTS

The above search initially returned 11 articles for review. After employing the inclusion and exclusion criteria, three articles remained that are included in this systematic review. All three of these articles are observational studies.

Wang et al

This study[1] was a pre/postexperimental study designed to analyze the effects of stereotactic surgery on AN patients. Two of the eight subjects underwent DBS of the nucleus accumbens (NAc), while the other six underwent ablation of the same area. The two subjects that underwent DBS were 28 and 18 years old with illness durations of 2 and 3 years and amenorrhea durations of 5 and 9 months, respectively. Outcomes included vital signs, BMI, menstruation, depression, anxiety, obsessive-compulsive symptoms, quality of life, intelligence, and memory.[1]

All subjects were recruited from the Tangdu Hospital in China between January 2007 and December 2009. Patients were included if they had a DSM-IV diagnosis of AN that had lasted at least 2 years, were over 18 years of age, had shown resistance to standard treatments, were deemed as being in a life-threatening situation by their doctor, and were physically eligible for

elective neurosurgery. Exclusion criteria included the presence of any contraindications to surgery, metabolic pathology interfering with eating or digestion (e.g., diabetes), psychotic disorder, or an inability to understand the interview questions or sign the consent.[1]

A DBS electrode was implanted inside the targeted NAc and stimulation was started 2 days after the surgery. The BMI of the two patients increased from 13.3 to 18.0 and 12.9 to 20.8 by 1 year postoperatively. In addition, basic vital signs (blood pressure, heart rate, and temperature) improved significantly and menstruation returned within 9 months. These were probably affected in part by an increased physiological drive to eat. Depression, anxiety, obsessive-compulsive, and psychoticism scores decreased while intelligence, memory, quality of life, and social functioning scores increased (see Table II). A p-value of less than 0.05 was considered significant. Assessors and psychologists were blinded to the treatment.[1]

Zhang et al

This observational study[35], which followed a pre/postexperimental design, looked to demonstrate the changes in brain glucose metabolism following DBS. Given that DBS targeted at the NAc has been accepted as a treatment for obsessive-compulsive disorder (OCD) and that AN and OCD share common mechanisms, the authors hypothesized that there may be a common abnormal brain region that contributes to the symptoms of both disorders. Six AN patients and 12 healthy controls were included in this study. Ages of the 6 subjects ranged from 13 to 17 and the duration of their disease ranged from 13 to 42 months. All were on at least one drug for their condition, including SSRIs, olanzapine, quetiapine, and aripiprazole. Outcomes included brain glucose metabolism, BMI and the need for drugs post-DBS.[35]

The study was approved by the medical ethics committee of Fudan University Huashan Hospital and Shanghai Jiaotong University Ruijing Hospital, both in China. All subjects had been diagnosed with restricting type AN and had failed conventional therapies. Healthy controls were included for comparison of brain glucose metabolism if they did not have a current axis I psychiatric disorder, had not taken psychotropic medications or hormones within the past six months, and had no history of neurological disease, head injury, or alcohol abuse.[35]

Glucose metabolism was examined via fludeoxyglucose (^{18}F) positron emission tomography (^{18}F-FDG PET) scans in the subjects. Four of the AN patients underwent NAc-DBS and had a follow-up scan three to six months after the surgery to assess changes. In the four AN patients that had DBS, glucose metabolism was found to decrease in the frontal lobe, bilateral lentiform nucleus, and hippocampus, which had been found to be the major differing areas from the healthy controls. In addition, BMI increased in all four subjects from a mean of 12.13 to 15.65 at one month and no drugs were required post-DBS.[35]

Lipsman et al

This study[4] was a phase I prospective trial to examine the safety and efficacy of deep brain stimulation on patients with treatment-refractory anorexia nervosa. Six patients were included, ages 24-57. The duration of their illnesses ranged from 4 to 37 years. All but one had psychiatric comorbidities, such as major depressive disorder (MDD), OCD, and post-traumatic stress disorder (PTSD) and all six had medical complications, including cardiac, endocrine, gastrointestinal, musculoskeletal and metabolic problems. The primary outcomes of this study as a pilot trial were any adverse events associated with the procedure. Its purpose was to evaluate the safety of the procedure before recommending further research in that area. Secondary

outcomes included weight (BMI) and mood and anxiety measures (Beck depression inventory (BDI), Beck anxiety inventory (BAI), Hamilton depression rating scale 17 (HAMD), Yale-Brown obsessive compulsive scale (YBOCS), and Yale-Brown-Cornell eating disorder scale (YBC-EDS)).[4]

Patients were recruited from Toronto General Hospital's eating disorders program along with community referrals. Inclusion criteria included males and females ages 20-60 (only females qualified) diagnosed with restricting or binge-purge type anorexia nervosa showing chronicity or treatment resistance. Subjects were excluded if they had a history of psychosis, neurological diseases, or alcohol or substance abuse in the past 6 weeks, contraindications to MRI or PET scanning, BMI of less than 13, or pregnancy. Baseline psychometric assessments and BMI measurements were performed along with MRI and ^{18}F-FDG PET neuroimaging.[4]

The subcallosal cingulate was the area of interest in this study due to similar patterns of activity shown across patients with other psychological disorders (e.g., depression, mood and anxiety disorders). This area was targeted with hopes that it would lead to a longer recovery than the treatment of weight alone, which has been shown to lead to a faster relapse. During the procedure, electrodes were inserted and an intraoperative AN rating scale designed by the research team was administered to monitor changes in symptoms with stimulation. They were placed in the areas that elicited the most relief from mood and anxiolytic symptoms or as near as possible to the subcallosal cingulate. The electrodes were then connected to a pulse generator, which was placed subcutaneously below the clavicle under general anesthesia.[4]

Several adverse events were noted during the study, the most serious being a seizure experienced two weeks postoperatively due to a metabolic derangement. The DBS device was

deactivated and turned back on 1 week later with no further problems. Other adverse events, including a panic attack, air embolus, and hypokalemia, were deemed non-study related and the procedure was considered to be safe. Three patients experienced pain associated with the surgical incision or positioning. At nine months, none of the subjects had experienced death, stroke, infection, or serious device-related complications.[4]

In reference to other outcomes measured in this study, BMI increased to a healthy range in three of the six patients by 9 months. Overall mean scores on depression, OCD, anxiety, and eating disorder (ED) scales significantly decreased and quality of life increased. More specifically, quality of life increased in those who saw an increase in BMI.[4]

DISCUSSION

According to the above evidence, DBS significantly improved outcomes in women with refractory AN. The Wang et al study[1] demonstrated the potential of DBS to increase the physical health, mental health, and cognitive level of the subjects and decrease common symptoms in AN. No serious adverse events were noted. The Zhang et al study[35] shed some light on the neural pathways involved in the disordered behaviors of people with AN. It helped to better define which areas lead to specific symptoms of the disorder. Improvement in these areas offer promise in the way of treatment of refractory AN if these locations can be targeted. Finally, the Lipsman et al[4] study showed that DBS as a treatment for AN is relatively safe and can lead to improvements in BMI and AN-associated symptoms. Most importantly, it demonstrated that DBS may disrupt important illness-maintaining factors and could be a solution for patients with refractory disease.

The results of the aforementioned studies have shown to be consistent. Outcomes measured were not identical across all three, but the results of each study were supportive of the others. Outcomes measured improved overall across the board and can be divided into those that pertain to physical health, psychological health, glucose metabolism, and safety of the procedure. The increase in physical health was made clear in multiple studies (see Tables II and III). In the three studies evaluated in this systematic review, 9 of the 12 patients that received DBS had a significant increase in their BMI.[1,4,35] In Wang et al[1], vital signs returned to a normal range and menstruation returned within nine months. None of the four patients in Zhang et al[35] required drugs after DBS, even though they had required them prior to the procedure.

Psychological health was also improved in the three studies examined (see Tables II and III). Symptoms of anxiety, depression, and obsession-compulsion were significantly decreased.[1,4,35] These are aspects of the disorder that increase the behaviors typical of the disorder and significantly decrease the quality of life in patients with AN. Lipsman et al[4] showed a positive effect of DBS on depression, anxiety, OCD, and ED symptoms. Wang et al[1] showed a positive effect on depression anxiety, OCD, psychotic, and neurotic symptoms and showed increased intelligence, memory, social functioning, and quality of life.

In addition, ten of the ten patients in which glucose metabolism was measured showed metabolic improvement in the targeted areas following DBS (see Tables II and III). These studies display important patterns of hyper- and hypometabolism. In addition, the changes that came with targeted DBS confirm the specificity of these patterns. These changes were appreciated as early as three to six months after the surgery.[4,35] If the underlying cause of the

symptoms and behaviors of AN can be targeted, it is possible that the root of the problem can be reached.

Lastly, only one of the patients that underwent DBS had a serious adverse effect that did resolve itself.[4] This offers promising proof that DBS is a relatively safe procedure and may open the door for further studies to be completed.

The main limitations of these studies.[1,4,25] included small sample sizes and a lack of control groups. The follow-up times in each study were short at 6 months,[35] 9 months,[4] and 1 year,[1] limiting the confidence that the results are long-lasting. Although Lipsman et al[4] had a control group, it was not an appropriate control group due to multiple variables and there was a lack of blinding in the study in order to maintain the safety of the patients. These limitations decrease the quality of the evidence but can be understood due to the high cost and invasiveness of DBS and the fact that these were pilot trials. Additionally, although the sample sizes were small, the treatment effect was quite significant, giving more credibility to the research. In addition, brain glucose metabolism, vital signs, and BMI as outcomes are very objective, also giving more validity to the research. Other outcomes, such as the mood scales, are more subjective, but showed a large treatment effect in most of the subjects.

One of the main concerns of these studies was the high cost of DBS. DBS generally costs between $35 000 and $50 000, with some bilateral procedures costing as much as $100 000 after accounting for anesthesia, hospital, device, and physician fees.[39] However, inpatient treatment costs upward of $1000 per day to cover for staff (including medical providers, therapists, nurses, dietitians, care staff, etc.), meals, and housing. This often does not include medications, lab processing, and outside consults.[40] Typically, patients require a stay of at least three to six

months, often returning for multiple stays with relapses. Though expensive, DBS may be more cost-effective in the long run and may get to the root of the problem faster than conventional treatments.

Further study in this area is recommended to continue to examine the effectiveness and safety of DBS in the treatment of AN. Randomized controlled trials with larger sample sizes are needed, especially now that the relative safety has been demonstrated. Comparisons can be made through RCTs between those receiving DBS and those receiving conventional treatments, although blinding may be difficult. The outcomes used in the studies in this review are fairly comprehensive given what is known about the effects of AN and could help show differences between the two treatments. Due to the large number of treatment centers in the United States, subjects could be recruited easily from inpatient centers or hospitals. Additionally, further study is needed to examine relationships between the response to DBS and patient demographics (e.g., age, duration of disorder, comorbid conditions, and type of AN). Further study of specific areas of the brain may also help better target the disorder in certain patients. Studies with longer follow-up times would also help determine whether or not the results are long-lasting. For example, one subject in the Lipsman et al[4] study had suffered from this disorder for 37 years. Ideally, future studies could follow these subjects for 10, 20, or even 30 years postoperatively to determine whether or not the effects of DBS wear off against the chronicity of this disorder.

CONCLUSION

DBS significantly improved outcomes in adolescent and adult women with refractory anorexia nervosa. Outcomes measured included body weight (measured by BMI), vital signs, return of menstruation, brain glucose metabolism, depression, OCD, anxiety and ED scores,

intelligence, memory, quality of life, and adverse events associated with the surgery. DBS was shown to increase BMI and improve vital signs. In addition, it decreased many of the psychological symptoms associated with the disorder, such as depression, OCD, anxiety, and ED behaviors while displaying a positive effect on intelligence, memory, and quality of life. It targeted and changed glucose metabolism in problem areas of the brain. Lastly, it was shown to be relatively safe with no significant adverse reactions. With more extensive and consistent research, this could offer a viable solution to a very difficult-to-treat condition, improving the lives of those who suffer from it and decreasing the amount of time and money spent on refractory treatment and multiple hospitalizations. In contrast to many of the conventional treatments used today, this treatment seems to target the root of the problem: how the brain is processing signals and information and may offer a great treatment for refractory AN in women. Although the evidence is limited and more research needs to be done, the effect of DBS on outcomes in adolescent and adult women with AN looks promising.

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Table I. Characteristics of Reviewed Studies, GRADE Profile

Quality Assessment									
		Downgrade Criteria						Quality	Importance
No. of Studies	*Design*	*Limitations*	*Indirectness*	*Imprecision*	*Inconsistency*	*Publication bias likely*	*Study/Studies*		
Body Weight (BMI)									
3	3 Observational	Very serious limitations[a]	No serious indirectness	Serious imprecision[b]	Serious inconsistencies[c]	No bias likely	Wang et al1 Lipsman et al[4] Zhang et al[35]	Very low	Critical
Vital Signs and Return of Menstruation									
1	1 Observational	No serious limitations	No serious indirectness	Serious imprecision[b]	No serious inconsistencies	No bias likely	Lipsman et al[4]	Very low	Critical
Psychological Symptoms (anxiety, depression, ED, OCD, psychoticism, neuroticism, intelligence, memory)									
2	2 Observational	Very Serious limitations[a]	No serious indirectness	Serious imprecision[b]	Serious inconsistencies[c]	No bias likely	Wang et al[1] Lipsman et al[4]	Very low	Important
Changes in Brain Glucose Metabolism									
2	2 Observational	No serious limitations	No serious indirectness	Serious imprecision[b]	No serious inconsistencies	No bias likely	Lipsman et al[4] Zhang et al[35]	Very low	Important
Safety of DBS									
2	2 Observational	Serious limitations	No serious indirectness	Serious imprecision[b]	No serious inconsistencies	No bias likely	Wang et al[1] Lipsman et al[4]	Very low	Critical
Quality of Life									
2	2 Observational	Very Serious limitations[a]	No serious indirectness	Serious imprecision[b]	Serious inconsistencies[c]	No bias likely	Wang et al[1] Lipsman et al[4]	Very low	Important

[a]Short follow-up times in all 3 studies and no control group in Wang et al[1] or Lipsman et al[4].
[b]Small sample size and large standard deviations in all 3 studies.
[c]Inconsistencies (failure of 50% of subjects to improve with treatment) in Lipsman et al[4] without sufficient explanation.

Tables II-III. Summary of Findings

TABLE II Wang et al[1]

Outcome	Pre-operative	Post-operative (1 week)	Post-operative (6 months)	Post-operative (1 year)	P value
BMI	13.31 (0.53)	13.71 (0.65)	18.90 (1.35)	20.14 (1.38)	
Vital Signs					
Blood Pressure (mmHg)	87.75/63.50 (6.69/4.38)	87.00/64.25 (5.13/2.31)	95.12/68.38 (3.6/1.77)	105.75/73.50 (4.59/1.60)	
Heart Rate (bpm)	52.63 (6.30)	53.25 (5.39)	63.13 (2.53)	72.00 (2.62)	
Temperature (°C)	35.71 (0.31)	35.76 (0.34)	36.05 (0.21)	36.43 (0.10)	
Obsession	8.63 (5.53)	3.88 (3.64)	2.88 (3.14)	2.38 (3.16)	0.01
Compulsion	7.13 (5.84)	3.38 (3.93)	2.38 (2.77)	2.38 (3.38)	
Depression[a]	19.13 (6.45)	9.13 (5.67)	5.38 (3.81)	5.38 (2.72)	0.001
Anxiety[b]	18.88 (9.64)	10.38 (10.74)	6.88 (7.04)	3.88 (3.09)	0.003
Intelligence[c]	91.25 (2.82)	--	101.50 (5.66)	112.25 (6.65)	<0.001
Memory[d]	83.38 (3.62)	--	92.63 (3.81)	96.88 (1.73)	<0.003

Values show mean with (standard deviations)
[a]HAMD
[b]HAMA
[c]Wechsler Adult Intelligence Scale-Revised Chines version
[d]Wechsler Adult Memory Scale-Revised Chinese version

TABLE III Lipsman et al[4]

Outcome	Baseline	Pre-operative	Post-operative (1-2 months)	Post-operative (3 months)	Post-operative (6 months)	Post-operative (9 months)	P value
BMI (Mean)	13.7	16.1	14.0	14.7	15.3	16.6	
Adverse Events	--	--	Reported,[a],but most related to the disease itself	--	--	--	
HAMD (Depression)	--	17.8 (8.2)	13.6 (6.6)	12.5 (6.6)	10.7 (8.4)	--	
BDI (Depression)	--	38.8 (23.2)	29.2 (6.2)	25.8 (18.3)	20.2 (20.4)	--	
YBOCS (OCD)	--	25.0 (10.9)	--	15.8 (6.2)	13.2 (6.9)	--	
BAI (Anxiety)	--	31.2 (18.8)	26.7 (13.9)	29.0 (18.5)	21.7 (14.1)	--	
YBC-EDS (ED Preoccupations)	--	23.7 (3.4)	22.2 (9.6)	19.7 (7.1)	17.7 (6.9)	--	
YCS-EDS (ED Rituals)	--	29.3 (3.7)	22.3 (9.9)	22.2 (6.8)	19.0 (9.5)	--	
Glucose Metabolism					Decreased[b] Increased[c]		<0.01
Quality of Life							
Overall	57.3 (25.6)	--	--	--	65.8 (20.1)	--	
Among Increased BMI Group	43.0 (10.0)	--	--	--	60.0 (7.5)	--	
Among Unchanged BMI Group	71.7 (30.4)	--	--	--	71.7 (29.1)	--	

Values show mean with (standard deviations)
[a]Pain, nausea, pancreatitis, hypokalemia, panic attack, seizure, delirium, hypophosphatemia, QT prolongation, worsening mood
[b]Anterior cingulate, medial frontal gyrus, bilateral insula, left caudate, left claustrum, and left cerebellum
[c]Posterior cortical regions, right middle and inferior temporal gyrus, left post-central gyrus, right precuneus, right supramarginal gyrus, right inferior parietal lobe, and left cuneus