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Brief Report

Naltrexone Reduces Binge Eating and Purging in Adolescents in an Eating Disorder Program

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Abstract

Objective: Little evidence exists for pharmacologic treatment of binge eating and purging in adolescents with eating disorders. Given the role of the opioid reward system in compulsive binge eating and purging, naltrexone, an opioid antagonist, may be effective in reducing these behaviors. Previous studies have demonstrated that naltrexone reduces binge eating and purging in adults, yet evidence for its use in adolescents is lacking. This case series describes naltrexone utilization, response, and safety in adolescents with eating disorders.

Methods: A retrospective chart review of adolescent patients prescribed naltrexone at an academic eating disorder program was completed.

Results: Thirty-three adolescents aged 15.3 ± 1.49 years, 94% female gender identity, were treated with naltrexone with the most common expected outcome ''to reduce vomiting.'' Naltrexone was prescribed for 129 ± 125 days. Over half of patients (52%, $n = 17$) had liver function tests during follow-up, all of which were within normal limits. Three patients (9.1%) experienced nausea related to naltrexone. Just over half of adolescents (67%; $n = 22$) had documentation of positive naltrexone response (e.g., reduced purging or urge to purge). The mean Clinical Global Impressions-Improvement score was 2.7 ± 1.3 (2 = much improved; 3 = minimally improved).

Conclusions: Naltrexone is safe, well tolerated, and effective for the treatment of adolescents with binge eating and/or purging as part of a comprehensive eating disorder treatment plan. Further study is necessary to confirm the effectiveness of naltrexone prospectively and evaluate factors contributing to naltrexone response vs. nonresponse to promote an individualized approach to treatment of binge eating and purging behavior.

Keywords: naltrexone, purge, binge eating, adolescents, neuropharmacology, psychopharmacology

Introduction

Eating disorders affect up to 1%–2% of adolescents, and lead to significant morbidity (e.g., cardiac compromise, malnutrition, osteopenia, substance abuse) and mortality (Franko et al. 2018; Hail and Le Grange 2018). The onset of these disorders occurs during adolescence, making this period of development an important time to recognize and effectively intervene in an attempt to reduce associated poor health outcomes.

Although each eating disorder diagnosis is distinct, they share an element of compulsive behavior (restricting, purging, and/or binge eating). The opioid system is implicated in the reward circuit that drives compulsive behavior. Evidence from both animal and human studies describes the role of the reward circuit in food palatability (e.g., binge eating) and pleasure (e.g., purge behaviors) (Frank 2013; Heal et al. 2017).

Naltrexone, an opioid antagonist, has been used to treat binge eating and purging associated with eating disorders in adults (Jonas and Gold 1988; Raingeard et al. 2004). Few controlled studies have been conducted, and there remains uncertainty regarding effective doses and treatment durations (Mitchell et al. 1989; Alger et al. 1991; Marrazzi et al. 1995). Across all studies, very few adolescents have been included, and no studies looked specifically at this unique population (Raingeard et al. 2004). Consequently, the utility of naltrexone in adolescents with eating disorders is unknown. Few evidence-based pharmacologic treatment options exist for adolescents with eating disorders. This case series is the first to describe naltrexone utilization and response patterns in an adolescent eating disorder center.

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Methods

This was a retrospective study of electronic health records for patients meeting inclusion criteria: prescribed naltrexone between 1/1/2010 and 09/30/2018 at a tertiary eating disorder center. There were no exclusion criteria. Data were captured from provider notes (diagnoses, reason for prescription, side effects, response, reason for naltrexone discontinuation), prescription records (naltrexone dose and duration), and laboratory results (liver function tests [LFTs] at baseline and at follow-up to assess for naltrexone safety). Tolerability was determined based on continued use by prescription refill, lack of documented naltrexone side effects, and CGI-I. Naltrexone response was assessed using the Clinical Global Impressions-Improvement (CGI-I) scale and was coded independently by two investigators (S.S. and W.A.). Discrepancies occurred in the rating of two participants and were resolved by accepting the most conservative rating. Participants missing documentation of naltrexone response ($n=5$) at the end of naltrexone duration were conservatively rated a CGI-I score of 5 (5 = minimally worse) to mitigate potential bias associated with omission.

The study was approved by the Institutional Review Board at Children's Mercy Kansas City.

SPSS version 24 (IBM Corp.) was used to perform descriptive statistics, chi-square (categorical data), and multivariable logistic regression (analysis of predictors of response) with *a priori* significance level set at $\alpha=0.05$.

Results

A total of 34 adolescents were prescribed naltrexone for an eating disorder during the study period. One patient with documentation of complete noncompliance (i.e., never took the medicine) was excluded; therefore, 33 adolescents were analyzed. Adolescents ranged in age from 12 to 19 years and weight from 40 to 113.5 kg. Female gender identity was endorsed in 94% ($n=31$). Additional clinical characteristics are detailed in Table 1.

Table 1. Study Demographics and Clinical Characteristics ($N=33$)

	Mean ± SD
Age, year	15.3 ± 1.49
BMI z-score	0.81 ± 0.86
BMI percentile	73.9 ± 22.1
Naltrexone duration, days	129 ± 125
Race	*n* (%)
White	24 (73)
Black	2 (6.1)
Hispanic	5 (15)
Asian	1 (3.0)
Other	1 (3.0)
Gender	
Female	29 (88)
Male	1 (3.0)
Male to female	2 (6.1)
Female to male	1 (3.0)
Eating disorder diagnosis	
Anorexia nervosa-binge/purge subtype	12 (36)
Bulimia nervosa	12 (36)
EDNOS/OSFED	8 (24)
Other	1 (3)
Comorbid diagnoses	
Generalized anxiety disorder	18 (55)
Attentive-deficit/hyperactivity disorder	4 (12)
Bipolar disorder	2 (6.1)
Major depressive disorder	19 (56)
Gender dysphoria	3 (9.1)
Nonsuicidal self-injury disorder	6 (18)
Obsessive compulsive disorder	1 (3.0)
Posttraumatic stress disorder (PTSD)	3 (9.1)
Substance use disorder	3 (9.1)
Concomitant medication use	
SSRI	27 (82)
Sertraline	9 (27)
Fluoxetine	15 (45)
Escitalopram/citalopram	4 (12)
Other psychotropics	10 (30)
Aripiprazole	3 (9.1)
Dex-/methylphenidate	2 (6)
Lisdexamfetamine	1 (3.0)
Quetiapine	2 (6)
Olanzepine	2 (6)
Guanfacine	1 (3.0)
Prazosin	1 (3.0)
Lamotrigine	1 (3.0)
Hormonal contraceptives	7 (21)
Combined oral contraceptive pills	5 (15)
Medroxyprogesterone	1 (3.0)
Cross-gender hormones (leuprolide, estrogen, and progestin)	1 (3.0)

SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; EDNOS/OSFED, eating disorder not otherwise specified, other specified feeding and eating disorders; BMI, body mass index.

Utilization of naltrexone

Naltrexone was prescribed at 50 mg/day in 97% ($n=32$) of adolescents. One patient was titrated to 100 mg/day. Prescription duration ranged from 28 to 600 days with a median of 90 days. The most commonly documented outcome expected by the provider was a decrease in vomiting or urges to vomit (58%; $n=19$), followed by a decrease in binge/purge or urge to binge/purge (18%; $n=6$). Nearly one-quarter of provider notes ($n=8$) lacked documentation of the target outcome. Naltrexone was used as the sole psychopharmacologic agent in 15% ($n=5$) of adolescents and as an adjunct to other psychopharmacologic agents in the rest of the cohort (Table 1).

Exploration into naltrexone response

Positive response to naltrexone was documented in 22 patients (67%) (Table 2). Nonresponse was coded in five patients who lacked documentation regarding response, and six patients with neutral or negative response (e.g., ''lack of change,'' ''does not report noticing a difference with [naltrexone]''). In the five adolescents taking naltrexone alone (i.e., no concomitant psychopharmacologic agent), positive response was documented in 80%. The mean CGI-I score was 2.7 ± 1.3 (2 = much improved; 3 = minimally improved). In a multivariate logistic regression model, no predictors of naltrexone response were identified. Test variables included concurrent use of selective serotonin reuptake inhibitor (SSRI), other psychotropic medications, or hormones; baseline weight or body mass index (BMI); comorbid anxiety, depression, bipolar, obsessive compulsive disorder, posttraumatic stress disorder, attentive-deficit/hyperactivity disorder, gender dysphoria, NSSI, or substance use.

Safety and tolerability of naltrexone

Thirty patients (91%) had documentation of LFTs at baseline, all of which were within normal laboratory range except for one

Table 2. Qualitative Analysis of Naltrexone Response

Naltrexone response category	*Qualitative statement documented in provider note*
Really helping; feels it's working	''Patient feels naltrexone is really helping and would like to continue.''
Reduced vomiting/urge to vomit	''No more vomiting, reduced urges''
	''Thinks that the Revia is helping her not think about throwing up''
	''Taking naltrexone daily, thinks this is also helping…She would like to stay on the naltrexone as she thinks it is still helping her with urges to vomit.''
	''She feels that the Revia is very helpful…has been able to decrease her vomiting of food to only 2 times in the last 2 weeks.''
	''She always wants to throw up, not now at every meal as in the past, but constantly has to fight the urge. She thinks that the Revia has been helpful some…She thinks the Revia is still helping her with the urges to vomit, but is still having these urges daily.''
Reduced purging/urge to purge	''Thoughts of purging improved with Revia.''
	''She continues to purge, but less frequent. Last episodes was 'weeks' ago, but couldn't remember the exact date. She says she feels 'awful' afterward. It no longer gives her the sense of calm.''
	''She says that she has only had the urge to purge her intake once since starting naltrexone and feels this has been a good addition.''

Statements above are representative statements reflecting the corresponding naltrexone response category. Revia is a trade name for naltrexone.

participant with alanine transferase (ALT) and aspartate transferase (AST) values 2 × upper limit of normal (105 and 105, respectively). Half of patients (52%, $n = 17$) had follow-up LFTs after initial naltrexone prescription, ranging from 3 weeks to 15 months of use, all of which were within normal laboratory limits. No elevations in LFTs were documented during naltrexone therapy. In fact, the individual with AST/ALT values 2 × upper limit of normal had follow-up AST/ALT values that fell within normal limits after 1 month of naltrexone use and maintained within normal limits after 8 months of use. Side effects attributed to naltrexone use were nausea ($n = 3$; 9%) and dizziness ($n = 1$; 3%). Two of the three patients discontinued use due to nausea, one of which retrialed the medication at a later date with no documented nausea. No other side effects were documented in association with naltrexone use. The majority (88%) of participants took naltrexone for >30 days.

Discussion

This study describes the use of naltrexone in an adolescent population for which few evidence-based pharmacologic options exist, and suggests that naltrexone has a place in the menu of options available to clinicians as they navigate the complexities of treating eating disorders. The majority of patients described in this study were receiving concomitant psychiatric treatment, including medications, most commonly SSRIs, and were prescribed naltrexone as an adjunct to reduce purging behavior or intrusive urge to purge.

Potential hepatotoxicity associated with naltrexone has been described. In our study, naltrexone, at a dose of 50 mg, was not associated with elevation of liver transaminases in patients who had follow-up laboratory testing during treatment. In addition, documented side effects were minimal. These findings are congruent with a recent meta-analysis, showing that naltrexone up to 250 mg does not increase the rate of serious side effects over placebo (Bolton et al. 2019). In addition, naltrexone was well tolerated with discontinuation due to intolerable side effect (e.g., nausea) in only one patient.

This collection of cases provides a first look at naltrexone response in adolescents with eating disorders. The documented naltrexone response rate in our study suggests a role for naltrexone treatment in adolescents. Interestingly, one adolescent required dose escalation before reaching documented response. Uncertainty about optimal dose has been present since Jonas and Gold's open label trial in adults published in 1988 comparing low dose (50–100 mg) with high dose (200–300 mg) naltrexone, and is worthy of further investigation in adolescents (Jonas and Gold 1988). In addition, a subset of patients with no reported response was present in our study. Factors predictive of response vs. nonresponse may inform treatment choice.

In this small cohort, the documented clinical factors explored (i.e., concurrent psychiatric medication, comorbid psychiatric diagnoses, weight, BMI) were not predictive of naltrexone response. Naltrexone, taken orally, is accompanied by significant variability in systemic exposure in adults (Verebey et al. 1976; Verebey 1981; Meyer et al. 1984; Mason et al. 2002; Dunbar et al. 2006). Individual differences in the way the body handles the drug (i.e., pharmacokinetics) may affect how much active drug is available to work at its target (i.e., opioid receptors). Certain factors such as delayed gastric emptying and delayed total gut transit time associated with anorexia and bulimia may lead to altered pharmacokinetics, specifically drug absorption and first-pass metabolism (Zipfel et al. 2006). Further exploration into variables associated with naltrexone response may inform who would most benefit from treatment and at what dose (i.e., a precision therapeutics approach).

Limitations are important to note when interpreting these results and are inherent in the retrospective design; however, the design chosen was appropriate to describe the utilization patterns of naltrexone, our primary aim. Findings from this study are limited to documentation, and therefore, may underreport certain elements (e.g., response and/or side effects) or overestimate aspects such as naltrexone duration. Naltrexone utilization was described in a real-world context. Thus, the patients included in this study were receiving treatment in a multidisciplinary, family-based outpatient tertiary setting and therefore, other elements of their care (e.g., concurrent psychotropic medications, behavioral therapy, family involvement in treatment) may contribute to change in eating disorder symptom burden. Our small study was likely underpowered to detect significant predictors of naltrexone response, hence further investigation is warranted.

Conclusion

In conclusion, this brief report describes the use of naltrexone in adolescents undergoing outpatient eating disorder treatment and

fills an important gap in knowledge regarding potential pharmacologic options for this unique group of patients. Low-dose (i.e., 50–100 mg) naltrexone was well tolerated, and associated with documentation of reduced purging or urge to purge in just over half of adolescents. Given its documented use, future controlled studies should aim to prospectively examine naltrexone response in adolescents who purge, to elucidate opportunities for individualized therapeutics to improve outcomes.

Clinical Significance

Few evidence-based psychopharmacologic treatments of eating disorders in adolescents exist, while significant morbidity and mortality from disordered eating remain. This case series of adolescents treated with adjunctive naltrexone within an eating disorder center is the first to show the effectiveness and safety of this pharmacologic option. Overall, naltrexone is well tolerated, and reduces pervasive eating disorder symptoms of binge eating, purging, and urges to do so, with no documented serious side effects. Future prospective study is warranted to further identify best use of naltrexone for adolescents with binging and purging disorders.

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Disclosures

No competing financial interests exist.

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