HHS Public Access

Author manuscript

Int J Eat Disord. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Int J Eat Disord. 2017 April ; 50(4): 447–450. doi:10.1002/eat.22704.

The Partial Dopamine D2 Receptor Agonist Aripiprazole is Associated With Weight Gain in Adolescent Anorexia Nervosa

Guido K.W. Frank, M.D.[1,2], **Megan E. Shott, B.S.**[1], **Jennifer O. Hagman, M.D.**[1], **Marissa A. Schiel, M.D.**[1], **Marisa Deguzman, B.S.**[1,2], and **Brogan Rossi, B.S.**[1]

[1]Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, Colorado

[2]Department of Neuroscience, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Abstract

Objective—Finding medication to support treatment of anorexia nervosa has been difficult. Neuroscience based approaches may help in this effort. Recent brain imaging studies in adults and adolescents with anorexia nervosa suggest that dopamine related reward circuits are hypersensitive and could provide a treatment target.

Method—Here we present a retrospective chart review of 106 adolescents with anorexia nervosa some of whom were treated with the dopamine D2 receptor partial agonist aripiprazole during treatment in a specialized eating disorder program.

Results—The results show that aripiprazole treatment was associated with greater increase in body mass index (BMI) during treatment.

Discussion—The use of dopamine receptor agonists may support treatment success in anorexia nervosa and should be further investigated.

Anorexia nervosa is a severe psychiatric disorder associated with food avoidance and life threatening weight loss that most commonly occurs in females (American Psychiatric Association., 2013). No medication has been approved for the treatment of anorexia nervosa (Frank & Shott, 2016). Basic science has suggested that dopamine receptor agonists support learning and behavior change in females who are underweight and in a low estrogen state (Frank, 2014). This could have relevance for anorexia nervosa treatment and improve psychotherapy outcomes in this disorder. Three case reports supported benefits from prescription of the partial dopamine D2 receptor agonist aripiprazole in adults and youth with the disorder (Aragona, 2007; Frank, 2016a; Trunko, Schwartz, Duvvuri, & Kaye, 2011). One retrospective study suggested that the combination of a serotonin reuptake inhibitor (SSRI) with an atypical antipsychotic might reduce anorexia nervosa related cognitions, but did not show benefits for weight gain (Marzola et al., 2015). Controlled

Corresponding Author: Guido K.W. Frank, M.D., Associate Professor, Department of Psychiatry, Director, Developmental Brain Research Program, University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, Gary Pavilion A036/B-130, 13123 East 16th Avenue, Aurora, CO 80045, Phone: 720-777-7909, Guido.Frank@ucdenver.edu.

Disclosure of Conflicts

The authors declare no conflicts of interest. All authors contributed significantly to this manuscript.

medication trials in anorexia nervosa are inherently difficult to conduct because those individuals tend to be less interested in taking medications (Hagman et al., 2011). In our specialized eating disorder treatment program we prescribe aripiprazole to adolescents who are highly resistant to engaging in psychotherapy. The families are aware that the medication is not FDA approved for anorexia nervosa. In this study we conducted a retrospective chart review to investigate whether treatment with aripiprazole would benefit weight gain in adolescent anorexia nervosa.

Methods

We requested approval from the Colorado Multiple Institutional Review Board and Children's Hospital Colorado to search electronic patient records from 2012 to 2015 years to identify individuals who had been treated for anorexia nervosa in our specialized eating disorder inpatient or partial hospital program (PHP). The inpatient stay is for medically unstable individuals who transition to PHP when able. All individuals program together regardless of level of care. From the records the following information was extracted: age, BMI, BMI percentile at admission and discharge, medication treatment on admission and discharge, duration of inpatient treatment, and duration of partial hospital treatment.

Chart selection was further limited to individuals who were admitted at $\leq 10^{th}$ BMI percentile and who were in the treatment program for at least 21 days. Those thresholds were chosen to ensure low weight individuals and allow any prescription of aripiprazole time to affect brain neurotransmitters (Czoty, Gage, Garg, Garg, & Nader, 2013). Furthermore, charts was inspected for diagnoses of major depressive or anxiety disorders that were supported by description of quality and number of symptoms to warrant diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association., 2013).

Food avoidance behaviors (FABs) were assessed with a locally developed scale that scores time needed to eat, cutting food in small pieces, smearing food, refusing food items and needing supplementation.

Demographic variables were assessed using independent t-tests and correlations using Pearson correlation coefficients. A mixed model repeated measures ANCOVA was used to test interactions between anorexia nervosa with and without aripiprazole prescription on the target variables BMI and BMI percentile on admission and discharge from the program including relevant factors and covariates and verified using bootstrapping.

Results

The data search resulted in 106 patients; 22 individuals started aripiprazole during treatment in the program and continued at time of discharge. Demographic values are reported in Table 1. Both groups were matched for age and had similar number of inpatient days. Number of days in PHP was higher in the aripiprazole group, not quite meeting statistical significance. BMI and BMI percentile on admission as well as level of FABs were similar on admission. The aripiprazole group had significantly higher proportion of patients that were diagnosed

with an anxiety or major depressive disorder. SSRI prescription on discharge was higher in the aripiprazole group.

Aripiprazole was prescribed either once or twice a day typically at a low dose (1–5mg daily dose) in order to capture partial agonistic properties (de Bartolomeis, Tomasetti, & Iasevoli, 2015). No patient was treated with aripiprazole on admission or any other antipsychotic.

In the no-aripiprazole group, age was positively correlated with discharge BMI ($r=0.534$, $p<0.001$) and negatively with discharge BMI percentile ($r=-0.478$, $p<0.001$). Number of days in PHP correlated positively with discharge BMI percentile ($r=0.258$, $p<0.013$). In the aripiprazole group, age correlated negatively with discharge BMI percentile ($r=-0.481$, $p<0.023$); anxiety diagnosis correlated negatively with discharge BMI.

BMI and BMI percentile were normally distributed. Age and number of days in PHP were included in the ANCOVA model as covariates, and depression diagnosis, anxiety diagnosis and SSRI prescription as factors. The mixed model ANCOVA indicated significant group by time interactions, the aripiprazole group had greater gain in BMI and BMI percentile compared to the no-aripiprazole group (Table 2).

Secondary statistical tests to investigate SSRI effects suggested in the aripiprazole group only that SSRI prescription was associated with lower discharge BMI (BMI 18.4 versus BMI 19.8, $p<0.001$).

Discussion

This retrospective chart review indicates that aripiprazole prescription may be associated with higher weight gain in adolescent anorexia nervosa compared to a control group that was not treated with aripiprazole. A retrospective study is less reliable than a randomized controlled trial and the results have to be viewed with caution. However, medication trials in anorexia nervosa are notoriously difficult to conduct and we are dependent on less stringent methods (Lock et al., 2011).

The most desirable treatment effect is weight increase. We therefore chose BMI and BMI percentile as the most meaningful primary outcome measures. The effects from aripiprazole prescription were by absolute BMI values modest (6% higher in the aripiprazole group), but the BMI percentile was about 20% higher at discharge compared to the no-aripiprazole group. The treatment groups were fairly well matched for age and days in treatment, and both variables correlated with BMI values. The aripiprazole group had higher comorbidity and SSRI treatment. Therefore those variables were included in the statistical model.

A previous study in adults with anorexia nervosa who were all treated with an SSRI suggested that augmentation with an atypical antipsychotic (aripiprazole or olanzapine) might be beneficial for anorexia nervosa. Specifically, the authors found that aripiprazole was associated with reduced eating disorder preoccupations and rituals; although that study did not show a significant effect on weight gain (Marzola et al., 2015). We did not have sufficient baseline and post treatment behavioral data to comment on for instance effects on

preoccupations in our study. Our study results do not support the hypothesis though that SSRI medication is associated with positive effects on weight gain.

Neurobiological research from our group suggests that anorexia nervosa is associated with heightened responsiveness in brain reward circuits and this may be due to a hyper-sensitive dopamine system (DeGuzman, Shott, Yang, Riederer, & Frank, 2017; Frank, 2016b; Frank et al., 2012). The dopamine partial agonist aripiprazole is thought to down-regulate dopamine D2 receptor activity. We believe that this action results in improved brain function (Czoty et al., 2013) and may aid the psychotherapeutic process. Most patients were initially admitted to inpatient level of care before transition to PHP. Treatment involved supervised meal support including parent training according to the family based treatment (FBT) model (Lock et al., 2010). All patients were on a dietician supervised meal plan and had to supplement for uneaten food. Our treatment approach is also geared toward explicit learning and conscious behavior change (Prochaska & DiClemente, 1983). In successful treatment patients can identify concrete steps to change behavior and put those steps into action. These processes require development of insight and extinction of existing fears relating to weight gain and body image. Research has shown that dopamine receptor agonists support learning and reduce anxiety in females at low weight and a low estrogen state, and we believe that aripiprazole prescription may have a crucial role in learning and behavior change by facilitating those processes (Frank, 2014). This may lead to less secret exercising or other forms of avoiding weight gain. The dopamine D2 receptor has also effects on energy homeostasis, leptin signaling and body composition and there could be metabolic mechanisms that promote weight gain as well (Kim et al., 2010; Perez Millan et al., 2014; Ramos, Meguid, Campos, & Coelho, 2005; Yoon & Baik, 2015). Such proposed mechanisms are speculative at this point however, and require further study.

Limitations

Retrospective chart reviews are not as stringent as randomized controlled studies and electronic record searches may not catch all patients. Group sizes were unbalanced affecting statistical power. Insufficient behavioral data for instance for cognitive rigidity were available. The chart review did not allow for reliable determination of restricting or binge-eating/purging subtype; however, the vast majority of patients in our program are of restricting type, receive a similar meal plan regimen, are similarly closely supervised and prohibited from binge-eating or purging behaviors. Aripiprazole is also an agonist on the serotonin 1A and antagonist on the serotonin 2A receptor, which could have contributed to the effects in this study.

In summary, this study supports that a dopamine D2 receptor partial agonist could be beneficial in weight gain in adolescent anorexia nervosa. We do not believe that every patient with this disorder needs to be or should be treated with aripiprazole, but it could be a beneficial intervention for individuals with more intense and rigid eating disorder cognitions and who have more difficulty tolerating the process of weight restoration. However, there is no consensus as to what neurotransmitter alterations contribute to the neurobiology of anorexia nervosa. We need more studies that investigate interventions such as aripiprazole

under more rigorous circumstances to better understand the underlying neurotransmitter mechanisms that could lead to improved treatment outcome of anorexia nervosa.

Acknowledgments

This work was supported by the NIMH grants MH096777 and MH103436 (both PI GKWF).

References

American Psychiatric Association. Desk reference to the diagnostic criteria from DSM-5. Washington, DC: American Psychiatric Publishing; 2013.

Aragona M. Tolerability and efficacy of aripiprazole in a case of psychotic anorexia nervosa comorbid with epilepsy and chronic renal failure. Eating and Weight Disorders. 2007; 12(3):e54–57. [PubMed: 17984630]

Czoty PW, Gage HD, Garg PK, Garg S, Nader MA. Effects of repeated treatment with the dopamine D2/D3 receptor partial agonist aripiprazole on striatal D2/D3 receptor availability in monkeys. Psychopharmacology (Berl). 2013; doi: 10.1007/s00213-013-3274-7

de Bartolomeis A, Tomasetti C, Iasevoli F. Update on the Mechanism of Action of Aripiprazole: Translational Insights into Antipsychotic Strategies Beyond Dopamine Receptor Antagonism. CNS Drugs. 2015; 29(9):773–799. DOI: 10.1007/s40263-015-0278-3 [PubMed: 26346901]

DeGuzman M, Shott ME, Yang TT, Riederer J, Frank GK. Association of Elevated Reward Prediction Error Response With Weight Gain in Adolescent Anorexia Nervosa. American Journal of Psychiatry. 2017; appiajp201616060671. doi: 10.1176/appi.ajp.2016.16060671

Frank GK. Could dopamine agonists aid in drug development for anorexia nervosa? Frontiers in Nutrition. 2014; 1:19.doi: 10.3389/fnut.2014.00019 [PubMed: 25988121]

Frank GK. Aripiprazole, a partial dopamine agonist to improve adolescent anorexia nervosa-A case series. International Journal of Eating Disorders. 2016a; 49(5):529–533. DOI: 10.1002/eat.22485 [PubMed: 26593328]

Frank GK. The Perfect Storm - A Bio-Psycho-Social Risk Model for Developing and Maintaining Eating Disorders. Frontiers in Behavioral Neuroscience. 2016b; 10:44.doi: 10.3389/fnbeh.2016.00044 [PubMed: 27014006]

Frank GK, Reynolds JR, Shott ME, Jappe L, Yang TT, Tregellas JR, O'Reilly RC. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology. 2012; 37(9):2031–2046. DOI: 10.1038/npp.2012.51 [PubMed: 22549118]

Frank GK, Shott ME. The Role of Psychotropic Medications in the Management of Anorexia Nervosa: Rationale, Evidence and Future Prospects. CNS Drugs. 2016; 30(5):419–442. DOI: 10.1007/s40263-016-0335-6 [PubMed: 27106297]

Hagman J, Gralla J, Sigel E, Ellert S, Dodge M, Gardner R, … Wamboldt MZ. A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study. Journal of the American Academy of Child and Adolescent Psychiatry. 2011; 50(9):915–924. DOI: 10.1016/j.jaac.2011.06.009 [PubMed: 21871373]

Kim KS, Yoon YR, Lee HJ, Yoon S, Kim SY, Shin SW, … Baik JH. Enhanced hypothalamic leptin signaling in mice lacking dopamine D2 receptors. Journal of Biological Chemistry. 2010; 285(12):8905–8917. DOI: 10.1074/jbc.M109.079590 [PubMed: 20080963]

Lock J, Brandt H, Woodside B, Agras S, Halmi WK, Johnson C, … Wilfley D. Challenges in conducting a multi-site randomized clinical trial comparing treatments for adolescent anorexia nervosa. The International Journal of Eating Disorders. 2011; doi: 10.1002/eat.20923

Lock J, Le Grange D, Agras WS, Moye A, Bryson SW, Jo B. Randomized clinical trial comparing family-based treatment with adolescent-focused individual therapy for adolescents with anorexia nervosa. Archives in General Psychiatry. 2010; 67(10):1025–1032. DOI: 10.1001/archgenpsychiatry.2010.128

Marzola E, Desedime N, Giovannone C, Amianto F, Fassino S, Abbate-Daga G. Atypical antipsychotics as augmentation therapy in anorexia nervosa. PloS One. 2015; 10(4):e0125569.doi: 10.1371/journal.pone.0125569 [PubMed: 25922939]

Perez Millan MI, Luque GM, Ramirez MC, Noain D, Ornstein AM, Rubinstein M, Becu-Villalobos D. Selective disruption of dopamine D2 receptors in pituitary lactotropes increases body weight and adiposity in female mice. Endocrinology. 2014; 155(3):829–839. DOI: 10.1210/en.2013-1707 [PubMed: 24424036]

Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. Journal of Consulting and Clinical Psychology. 1983; 51(3):390–395. [PubMed: 6863699]

Ramos EJ, Meguid MM, Campos AC, Coelho JC. Neuropeptide Y, alpha-melanocyte-stimulating hormone, and monoamines in food intake regulation. Nutrition. 2005; 21(2):269–279. DOI: 10.1016/j.nut.2004.06.021 [PubMed: 15723758]

Trunko ME, Schwartz TA, Duvvuri V, Kaye WH. Aripiprazole in anorexia nervosa and low-weight bulimia nervosa: case reports. International Journal of Eating Disorders. 2011; 44(3):269–275. DOI: 10.1002/eat.20807 [PubMed: 20186719]

Yoon YR, Baik JH. Melanocortin 4 Receptor and Dopamine D2 Receptor Expression in Brain Areas Involved in Food Intake. Endocrinol Metab (Seoul). 2015; 30(4):576–583. DOI: 10.3803/EnM.2015.30.4.576 [PubMed: 26790386]

Int J Eat Disord. Author manuscript; available in PMC 2018 April 01.

Table 1

Demographic variables.

	AN (n=84)		AN Aripiprazole (n=22)		t	p
	Mean	**SD**	**Mean**	**SD**		
Age (years)	14.4	2.5	15.0	2.2	−1.125	0.263
Days in Inpatient Treatment	15.9 (n=69)	9.7	18.9 (n=16)	13.4	−1.049	0.297
Days in Partial Hospital Treatment	34.3	12.8	40.4	16.7	−1.890	0.061
Food Avoidance Behaviors Admission	2.8	3.7	3.4	2.3	−0.727	0.469
					Chi-Square	**p**
Patients in Inpatient Treatment	69 (83%)		16 (73%)		0.004	0.948
Anxiety Diagnosis	38 (45%)		16 (73%)		7.277	0.009
Depression Diagnosis	26 (31%)		14 (64%)		7.926	0.007
SSRI Prescription Discharge	44 (52%)		16 (73%)		4.830	0.033
Aripiprazole Dose (mg)			3.59	1.85		

Table 2

Mixed model ANCOVA results for Body Mass Index (BMI) and BMI percentile across groups at time of admission and discharge from treatment.

	AN		AN Aripiprazole		ANCOVA		Repeated Measures Group by Time Point Interaction			
	Mean	SD	Mean	SD	F	p	F	p	Partial η^2	Power
Admission BMI	15.1	1.5	15.6	1.3	0.966	0.328	5.968	0.017	0.064	0.676
Discharge BMI	17.9	1.4	18.8	1.4	4.578	0.035				
Admission BMI Percentile	3.1	3.0	4.2	3.7	1.840	0.178	5.529	0.021	0.060	0.479
Discharge BMI Percentile	28.6	16.9	36.4	16.3	5.624	0.020				