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REVIEW ARTICLE

Medical Complications of Eating Disorders: An Update

ELLEN S. ROME, M.D., M.P.H. AND SETH AMMERMAN, M.D.

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Eating disorders continue to be a prevalent problem in modern society, with serious, potentially life-threatening consequences. Anorexia nervosa (AN) is estimated to affect 1% of all children, adolescents, and young adults, bulimia nervosa (BN) is found in 1% to 19% depending on population surveyed, and "eating disorder not otherwise specified" (EDNOS) is found in as many as two-thirds of college athletes and other high risk groups [1–4]. The medical complications caused by eating disorders involve almost all organ systems and can be viewed in terms of consequences of: (a) starvation, (b) purging behaviors, and (c) binge eating. This article will review the medical complications as they affect various organ systems in patients with eating disorders. An overview of these medical effects is outlined in Table 1.

Cardiac Complications of Eating Disorders

Starvation can result in wasted cardiac muscle, sinus bradycardia, hypotension, and reduced left ventricular mass, associated with systolic dysfunction [5]. At a microscopic level, myofibrillar atrophy and destruction may result in decreased contractile force and cardiac output [6]. Patients with AN may complain of marked fatigue and have an attenuated blood pressure response to exercise with a reduction in maximal work capacity [7,8]. One-third may have mitral valve prolapse, from wasted cardiac muscle disproportionate to mitral valve size [9,10]. Cardiac vagal hyperactivity appears to be related to percent weight loss and significantly contributes to bradycardia [11]. Caffeine and exercise should be avoided to prevent a fatal arrhythmia in a patient with a wasted heart muscle and bradycardia, defined as a daytime heart rate under 50 beats per minute (b/m) and nighttime heart rate under 46 b/m.

Orthostatic hypotension (as manifested by pulse and/or blood pressure changes), sinus bradycardia, and hypothermia can be observed in patients with AN as well as those with BN. In the latter case, the patient need not be underweight or have lost weight to have orthostatic hypotension. These vital sign abnormalities are presumed to be adaptive in nature, a response to the decrease in basal metabolic rate that stems from diminished energy intake (e.g. insufficient ingested calories) [12]. Possible mechanisms include an autonomic imbalance in heart rate regulation, with reduced sympathetic activity and elevated vagal activity [13], and altered arterial baroreceptor reflex sensitivity resulting in excess vagal activity [11].

Electrocardiographic findings include sinus bradycardia with low voltage owing to nutritional restriction and/or compulsive overexercising. ST segment depression, T wave flattening, rightward QRS axis, and prolonged QTc interval are also associated with malnutrition, hyopkalemia, or other electrolyte disturbance. Accordingly, these electrocardiogram

From the Section of Adolescent Medicine, Cleveland Clinic Foundation, Cleveland, Ohio (E.S.R.); and the Division of Adolescent Medicine, Stanford University Medical Center, Stanford, California (S.A.).

Address correspondence to: Ellen S. Rome, M.D., M.P.H., Cleveland Clinic Foundation, 9500 Euclid Avenue, A120, Cleveland, Ohio 44195. E-mail: romee@ccf.org

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Table 1. Medical Complications of Eating Disorders

Effects of starvation
Amenorrhea (primary or secondary)
Atrophic vaginitis
Breast atrophy
Cardiac muscle wasting
Constipation
Decreased antidiuretic hormone secretion
Delayed puberty
Euthroid sick syndrome
Hypercholesterolemia
Hypercortisolemia
Hypophosphatemia
Increased basal growth hormone
Osteopenia
Pancytopenia
Persistence or resumption of prepubertal pattern of gonadotropin secretion
Vital Sign abnormalities
Bradycardia: Pulse <50 beats/min daytime or 45 beats/min overnight
Hypothermia: Temperature <36.3C daytime or ≤36.0C overnight
Hypotension: Systolic blood pressure <90 mm Hg or diastolic blood pressure <45 mm Hg
Orthostasis: Pulse increase >35 beats/min or blood pressure decrease >10 mm Hg
Effects of purging
Cardiac arrhythmia
Chronic hypovolemia
Chronic metabolic acidosis (with laxative abuse)
Chronic metabolic alkalosis (with vomiting)
Dental enamel erosion
Esophagitis
Hypocalcemia
Hypokalemia
Hypokalemic nephropathy with a urine-concentrating deficit
Hypomagnesemia
Hypophosphatemia
Mallory-Weiss tears
Parotid gland swelling
Pneumothorax or pneumomediastinum
Pseudo-Bartter's syndrome
Russell sign (callous on knuckles from finger use for inducing vomiting)
Secondary hyperaldosteronism
Vital Sign abnormalities
Effects of binging
Esophageal rupture
Gastric rupture

(ECG) changes may occur among patients who purge either with the purging type of AN, with BN, or with EDNOS. Because prolonged QTc can be life-threatening, an initial ECG is warranted in all patients with bradycardia. The risk for sudden cardiac increases when the QTc interval exceeds 470 milliseconds [14]. In a recent study, adolescents with eating disorders were no more likely than controls to exhibit prolonged QTc; the authors speculate that the increased rates of QTc prolongation particularly among adult patients with AN may reflect duration of illness on myocardial damage [15]. Moreover, a normal QTc interval should not reassure the clinician that the patient is not significantly ill. Relative bradycardia and decreased amplitude in V6 correlated significantly with lower body mass index, making these findings more useful electrocardiographic markers of disease severity [15]. With the exception of the irreversible myocarditis associated with emetine toxicity (seen with chronic ingestion of syrup of ipecac to induce vomiting), most cardiac findings in patients with eating disorders appear to be reversible with refeeding and weight stabilization. However, in a 1947 study of 32 men enduring experimentally induced semistarvation for 6 months, most cardiovascular measurements had returned to pre-starvation values after 32 weeks of nutritional rehabilitation; Keys noted that the oxygen provided per heart beat, as based on metabolic rate/pulse rate, did not attain pre-starvation measurements [16]. In a recent study, adolescent girls admitted to an inpatient unit with AN showed impaired exercise capacity, with significant ECG changes and/or arrhythmias revealed during their exercise studies [17]. The main factors affecting performance during exercise stress testing included rapidity of weight loss and percent body weight loss before testing. Although girls who were athletes before the onset of AN did better than nonathletes, 40% of the athletes displayed significant impairment, as opposed to 75% of the nonathletes. The extent of reversibility of cardiac function with prolonged nutritional deprivation remains to be seen.

Fluid and Electrolyte Changes

Refeeding Syndrome

The risk for cardiac decompensation is highest during the initial stages of refeeding, when left ventricular mass and contractility are already compromised by chronic starvation in patients with AN. "Refeeding syndrome" refers to cardiovascular collapse and possible death that follows oral or parenteral intake of highly caloric nutrients, especially those high in glucose [6]. Delirium can occur during, or after, the second week of refeeding and may continue for several weeks [14,18,19]. The mechanism of cardiovascular collapse presumably involves a shift of phosphate from the extracellular to the intracellular space after ingestion or infusion of glucose with

resultant stimulation by insulin. This shift from the catabolic state of starvation to an anabolic state of refeeding causes intracellular phosphate to be incorporated into newly synthesized tissues, specifically: (a) as phospholipids in the cell membranes of newly forming cells, (b) as phosphorylated intermediates necessary for protein synthesis and glycogen formation, and (c) through production of adenosine triphosphate (ATP) [18]. Total body phosphate depletion results in a depletion of ATP, resulting in depressed cardiac stroke volume [20]. This situation creates increased circulatory demands with a nutritionally depleted cardiac mass. Additionally, the refeeding syndrome can adversely affect many other organ systems, because ATP is a universal cell substrate. Kohn et al note that correction of serum phosphate does not appear to ameliorate delirium [18].

The refeeding syndrome can be prevented by starting refeeding slowly (e.g. 1500 calories/day (cal/d) initially, adding 100–250 cal/d for each day that the patient does not gain .2 kg/day while hospitalized). To avoid phosphate depletion, supplemental phosphorus (e.g., Nutra-phos 500 mg) orally twice a day for the first five days of refeeding can compensate for the increased tissue phosphate needs. Refeeding syndrome is more rare in the outpatient setting as patients do not tend to resume eating at 1500 calories or more per day on their own. They are more likely to overestimate what they are actually consuming and gain weight at a slower rate of .25 to 1 kilogram per week, rather than the average of .2 kg/day expected while hospitalized.

Electrolyte Abnormalities

Serum electrolyte measurement can be useful to screen for abnormalities such as hypokalemia, hyponatremia, and metabolic acidosis or alkalosis. Although the results may be normal despite frequent vomiting or laxative use, an elevated bicarbonate level combined with hypokalemia, which usually does not occur with caloric restriction alone, can be a useful clinical clue that the patient is surreptitiously vomiting or using diet pills [21,22]. Non-anion-gap acidosis can occur with laxative abuse [4]. Hyponatremia can occur with excess water intake or with inappropriate regulation of antidiuretic hormone (see section on water intoxication). Hypoglycemia can occur in patients with AN at low weight who may not recognize symptoms. Anecdotally, a subgroup of medically compromised patients report feeling "normal" when they experience weakness, dizziness, or lightheadedness, and may actively restrict or purge when not perceiving these symptoms.

Renal Abnormalities

Transient azotemia, decreased glomerular filtration rate, decreased concentrating ability, short periods of acute renal failure, and, more rarely, chronic renal failure have been noted in patients with eating disorders [23–25]. Those patients experiencing higher percentages of weight reduction and low body mass index may be at risk for borderline decreases in renal function even with normal levels of serum creatinine [26]. Four adult patients (aged from 31 to 43 years) developed end stage renal disease requiring chronic dialysis, each diagnosed with an eating disorder 10 to 20 years previously with ongoing symptoms [24]. These patients also displayed longstanding hypokalemia, hyponatremia, acid base disturbances, including hyperchloremic metabolic acidosis, and hypochloremic metabolic alkalosis. Other common electrolyte abnormalities include hypocalcemia, hypomagnesemia, and hypophosphatemia. The elevation of blood urea nitrogen levels can be prerenal and will respond to correction of renal perfusion by expansion of extracellular fluid volume with isotonic saline. However, these patients rarely require any intravenous fluids despite evidence of prerenal azotemia for the following reasons: (a) fluid and electrolyte compensation is safe and effective orally, given in appropriate doses with avoidance of hypophosphatemia as mentioned previously; and (b) rapid rehydration in a chronically compensated state may precipitate congestive heart failure in the dehydrated, compromised patient. Hypophosphatemia secondary to inadequate oral intake may precipitate rhabdomyolysis and acute renal failure; the latter is usually reversible after short-term dialysis. Rarely, chronic renal failure may develop in patients with eating disorders and should be a cause of grave concern [24].

Urine potassium levels less than 15 meq/L in the face of significant hypokalemia suggest extrarenal loss of potassium from the gastrointestinal tract as seen with laxative abuse [27]. Severe hypokalemia combined with a random urine sample containing 30 meq/L or more of potassium may indicate diuretic abuse [27]. Urine electrolytes have been found to be a useful marker for BN, with a ratio of urine sodium to urine chloride >1.16 identifying 51.5% of patients with BN with a 5% false-positive rate [28].

Water Intoxication

Many patients with AN "water load," either to blunt appetite by creating a sensation of fullness, to falsely elevate weight for medical visits, or in the misguided belief that consumption of water will purify the body and eliminate "toxins" and calories through the urine [25,26]. Water intoxication can cause severe hyponatremia and hypo-osmolality, which can produce cerebral edema, leading to ataxia, seizures, coma, and death [29,30]. As with many of the self-destructive behaviors of eating disordered patients, water overloading may continue despite awareness of the medical risks.

Gastrointestinal and Oropharyngeal Effects

Gastrointestinal (GI) effects of starvation include: delayed gastric emptying, slowed gastrointestinal motility, abnormal esophageal motor activity, and abnormal hormonal and neurotransmitter functions [31–37]. Prokinetic drugs such as cisapride or metochlopromide may relieve some of gastrointestinal symptoms, although the former is not currently used in the United States [38]. Gastrointestinal symptoms may persist after recovery from eating disorders [39], although they tend to substantially decrease with refeeding and weight restoration [40]. Also, adults with functional gastrointestinal disorders are more likely to have had a past eating disorder than are those with gallbladder disease (prevalence of past eating disorder 15.7% vs. 3.1%) [39]. Most patients will complain of constipation, early satiety, and bloating, all of which are symptoms that tend to inhibit further oral intake. Improved compliance with nutritional rehabilitation may be achieved when patients are provided with explanations of why and how their physical symptoms occur. For instance, the clinician can explain that prolonged starvation leads to slowed movement through the GI system, allowing the body to draw out all nutrients, as well as all possible water, leading to more constipation and more time for food to be broken down into gas, causing further bloating. Increased oral intake will eventually speed up transit through the gut, improving both bloating and constipation. Colonic transport has been shown to return to normal after patients consume a balanced diet or weight maintenance diet for at least 3 weeks [41]. Chronic laxative abuse can cause degeneration of the ganglion cells of Auerbach plexuses, aggravating the constipation associated with starvation [27]. When laxative ingestion is abruptly ceased, extreme fluid shifts and edema can occur within 24 to 36 hours, with weight gains of up to 10–20 pounds (5–10 kg) during that short time interval. Some clinicians recommend a laxative taper rather than abrupt cessation to avoid these extreme fluid shifts. Others choose to stop laxatives abruptly at time of admission with close monitoring for extreme fluid shifts. Both styles attempt to reinforce a message that laxative abuse can be deadly. Hypokalemia may also be an indirect finding of laxative abuse, as mentioned previously.

Binge eating has been associated with acute gastric dilatation and rupture, as well as esophageal rupture. Rectal prolapse with rectal bleeding was reported in seven women with BN [42]. Proposed mechanisms include any combination of constipation, laxative use, overzealous exercise, and increased intraabdominal pressure from self-induced vomiting.

No increased prevalence of *H. pylori* was found in 32 patients admitted for inpatient treatment of AN or BN [43], nor has *H. pylori* has been found to be the cause of dyspeptic symptoms in adolescents with eating disorders [44].

Cholesterol levels may be falsely elevated in some patients with eating disorders during prolonged starvation. At least three possible etiologies for the elevated cholesterol levels are reported: (a) depressed levels of triiodothyronine (T3) levels affecting cholesterol breakdown, (b) low cholesterol-binding protein levels, and (c) fatty infiltration of the liver causing leakage of intrahepatic cholesterol into the peripheral circulation [3,21].

Vocal cord pathology, including edema, telangiectasia, polypoid changes, and dysphonia, have been observed in patients with BN, with accompanying laryngopharyngeal reflux [45,46]. Presenting complaints can include persistent hoarseness, sore throat, frequent throat-clearing, and decreased pitch and recurrent loss of voice in singers. Fewer than half of patients with vocal cord pathology had symptoms of heartburn despite significant laryngopharyngeal reflux [46].

Reproductive Health Issues

Amenorrhea, Osteopenia, and Eating Disorders: The Female Athlete Triad

The Female Athlete Triad refers to the inter-relatedness of amenorrhea, osteopenia, and disordered eating. Athletes with a healthy body image and no evidence of disordered eating may still have athletic

amenorrhea. Athletic amenorrhea tends to occur most frequently in females who combine intense physical training with a low stable caloric intake working toward a desired lean body build, as is idealized in gymnastics, ballet, endurance running, or figure skating [47]. In the athletic female with AN, the goal of weight loss, in and of itself, becomes more important than the goal of improving athletic performance.

Amenorrhea is thought to be the result of hypothalamic suppression; it is unclear if the relative inadequacy of their caloric intake or the "stress" of their overly demanding exercise regimen, or the combination of both factors, is responsible for the hypothalamic suppression. Athletic amenorrhea reflects a hypoestrogenic state caused by hypothalamic suppression and is associated with delayed or interrupted puberty with decreased bone density in teens [48,49].

Approximately 40% to 60% of bone mass deposition occurs during the pubertal growth spurt in girls aged 11 to 14 years, a time when eating disorders may peak in prevalence. Peak bone mass is usually attained by late adolescence or early adulthood, but an additional 5% may be obtained during the third decade [50]. Even small differences in bone density have clinical significance; a 5% increase significantly decreases fracture risk whereas a 10% decrease in adult bone mineral density is associated with a two- to three-fold increase in fracture risk [50]. Weight gain has been associated with increased trabecular bone deposition, with positive correlations shown among calcium intake, physical activity, and bone deposition [51,52]. However, excess exercise in the context of an eating disorder and amenorrhea results in osteopenia.

Osteopenia that occurs with prolonged amenorrhea has been associated with increased risk of stress fractures in both athletes and patients with eating disorders [53,54]. Increased resorption of bone occurs with hypoestrogenism and hypercortisolemia; the latter is seen in patients with chronic stress. Decreased bone formation occurs with both glucocorticoid excess and insufficient dietary calcium and protein intake. Excess glucocorticoids may decrease calcium absorption from the gut and inhibit bone formation through direct, receptor-mediated osteoblast effects [55,56].

Dual X-ray absorptiometry (DEXA) allows accurate measurement of bone mineral density in areas of trabecular (spongy) bone. Spinal bone mineral density in AN inversely correlates with the degree of emaciation, especially with a body mass index below 15 kg/m^2 [57]. In a study of 51 Japanese female patients with AN, 29 of these young women evaluated longitudinally for 11 to 46 months, a modest but significant increase of bone mineral density (BMD) was detected when body mass index (BMI) was greater than 16.4 + .3 kg/m2, even when the patient remained amenorrheic. In this same study, no biochemical or endocrinological parameters significantly correlated with BMD, including serum osteocalcin, urinary degradation products of collagen I, serum total protein, albumin, calcium, alkaline phosphatase, plasma levels of intact parathyroid hormone, T3, growth hormone, insulin-like growth factor, cortisol, estradiol, and urinary free cortisol measured [57]. In a study of 69 patients referred to an eating disorders clinic in Western Australia, patients with AN were found to be more malnourished but with BMDs similar to DEXA results from other dieting patients. Patients with low bone density had dieted for longer periods of time, had lower lean body mass, and more often had not achieved menarche, with longer duration of secondary amenorrhea if postmenarchal, and lower estrogen levels [58] Risk factors for osteopenia are seen in Table 2.

Table 2. Risk Factors for Osteopenia in Patients With Eating Disorders

Absence of weight gain for prolonged period of time
Caucasian > African-American
Early onset of amenorrhea
Longer duration of hypogonadal state (amenorrhea)
Low protein intake
Low calcium intake
Smoking

Many questions remain with respect to treatment with estrogen and reversibility of low bone density. The role of estrogen replacement therapy in varying forms (oral vs. patch), alone or in combination with a progestin, remains unclear. Weight gain in patients with AN appears to reverse the trend of ongoing bone loss. There may be a subset of extremely underweight patients (weight less than 70% of ideal body weight) in whom estrogen replacement therapy may be of some benefit even before weight recovery [59]. Estrogen supplementation does not appear to decrease the incidence of pathologic fractures among osteopenic patients with AN. Newer agents such as dehydroepiandrosterone (DHEA) may have some role in preservation of BMD in the severely underweight patient with AN [60,61]. The bisphosphonates and growth hormone are also being evaluated as a form of treatment for osteopenia in adolescent

and young adult patients with eating disorders [62]. Questions remain as to the ideal form (patch vs. pill), amount, and duration of hormonal therapy, with further studies ongoing and necessary to clarify these issues. Because malnutrition is the primary cause of amenorrhea and decreased bone mineral density, normalization of nutrition is the recommended treatment for these problems.

Future Fertility in Women With a History of Eating Disorders

In a study of 66 women with a history of AN compared with 98 randomly selected community controls, there was no difference in rate of pregnancy, mean number of pregnancies per woman, or age at first pregnancy; however, more miscarriages (30% vs. 16%) and more cesarean deliveries (16% vs. 3%) occurred in the eating disorder group [63]. Offspring of women with AN may be of lower average birth weight and are more likely to be premature [63,64]. Counseling of girls and women with eating disorders should include recommendation for intensive prenatal care with a focus on adequate nutrition, even if the history of eating disorder is remote [63].

Other Endocrine Effects

Despite normal levels of adrenocorticotropic hormone, hypercortisolemia has been seen in AN patients and is associated with osteopenia [65,66]. This hypercortisolemia does not suppress with dexamethasone in these patients [67]. A euthyroid sick syndrome can occur, with lowered triiodothyronine levels, low thyroxine levels, and elevated reverse T3 [66,68]. Thyroid abnormalities can also be seen as refeeding is started; thyroid hormone replacement therapy is not indicated in these patients and may actually be used surreptitiously in rare patients to promote further weight loss.

Growth hormone (GH) levels have been found to be high in adolescents with AN, although insulin-like growth factor 1 (IGF-1) has been found to be low, suggesting a state of growth hormone resistance [69]. Pituitary GH secretory burst frequency, GH burst mass, and GH burst duration have been shown to be increased in women with AN as compared with normal weight healthy women, with a four-fold increase in 24 hour pulsatile GH secretion and a twenty-fold increase in nonpulsatile secretion or basal GH secretion rate [70]. GHRH-stimulated growth hormone release has been shown to be increased in patients with AN [71]. The mechanism may involve increased hypothalamic cholinergic activity with subsequently decreased somatostatinergic inhibition [72].

Individuals with AN display impaired release of vasopressin, consistent with partial diabetes insipidus. These patients will concentrate their urine appropriately when given vasopressin, suggesting a neurogenic defect causing the impaired release [73]. As with the other endocrine findings mentioned above, these findings are reversible with weight gain.

Hematologic Effects

Pancytopenia can be seen in patients with eating disorders. In one study, a relative leukopenia occurred in 23% of patients who were in a state of starvation, caused primarily by increased margination of the white blood cells [21,73]. Accordingly, patients do not have increased susceptibility to infection. Anemia is less common than leukopenia owing to the high prevalence of amenorrhea; however, a microcytic anemia can be seen in vegetarian patients, and hemoglobin levels may be falsely elevated in the face of dehydration. The erythrocyte sedimentation rate tends to be normal or low; an elevated value should trigger further investigation for an underlying medical cause (e.g., inflammatory bowel disease).

Effects on the Brain

Recent research has focused on the cerebral atrophy and loss of brain volume that accompanies AN [74,75]. In protracted cases of individuals with AN in a state of prolonged malnutrition, enlargement of the cortical sulci and cisterns, ventricular dilatation, and pituitary gland atrophy can occur [76]; these findings may, or may not, be reversible with recovery [75,76,78,79]. Some patients may have concomitant cerebral and cerebellar atrophy [80]. Hypothesized mechanisms to explain these observations include changes in the permeability of blood vessels, protein loss with movement of intracellular fluid toward extracellular spaces, inhibition of brain protein synthesis, cerebral dehydration owing to increased plasma cortisol levels, or low T3 levels [81]. Cognitive changes found in low weight patients may not completely resolve with refeeding [82].

In patients with BN, a global and regional absolute hypometabolism of glucose has been described

Table 3. Dermatologic Findings in Patients With Anorexia Nervosa and Bulimia Nervosa

Findings caused by caloric restriction
Acrocyanosis
Brittle nails
Bruising/hematomas
Diffuse effluvium (hair loss)
Lanugo hair
Peripheral edema
Split, dry hair without shine
White dermographism
Xerosis
Findings caused by self-injurious behavior
Scars (self-abusive behavior)
Onychophagia (nail biting)
Findings caused by self-induced vomiting
Decayed teeth
Russell sign (calloused knuckles from self-induced vomiting)

[83]. Patients with AN have been shown to display an absolute hypometabolism of glucose, as well, but with a relative hypermetabolism of glucose in the basal ganglia possibly owing to a more pronounced reduction in cortical than in basal ganglia glucose metabolism [81].

Other Medical Findings

Acquired *pili torti*, a structural hair defect that means "twisted hair," has been seen in patients with AN [84]. This finding may be associated with malnutrition combined with excess intake of yellow vegetables and vitamins. Increased levels of serum carotene, retinyl esters, retinol, and retinoic acid were found in a series of 14 patients who demonstrated pili torti. Other dermatologic findings associated with starvation include alopecia, xerosis, hypertrichosis, and nail fragility [85].

An association may exist between atopy and eating disorders, with an increase in serum IgE levels found in 30% of patients with AN and 52% of patients with BN [86,87]. Dermatologic findings are listed in Table 3.

Conclusion

The medical complications of eating disorders are significant and potentially irreversible and life-threatening. Moreover, careful explanation of the medical changes that occur when a patient has an eating disorder may help patients make positive changes. Further research is needed to clarify the role of hormone replacement therapy and the use of the bisphosphonates, DHEA, and other newer drugs to treat osteopenia in patients with eating disorders.

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