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State of the Art

Appetite Stimulants Use in Cystic Fibrosis

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Summary. Cystic fibrosis (CF) is an autosomal recessive disease. It affects multiple body organs. The lungs and pancreas are the most affected which results in progressive lung damage and pancreatic insufficiency. Due to the disease process, CF patients require significantly higher caloric intake than recommended for other individuals. The nutritional goal for CF patients is to achieve normal growth and development and, once genetic potential is reached, to maintain good nutritional status throughout life. Evidence has shown that lung function is closely associated with nutritional status in CF and that nutritional status is an independent predictor of survival. Most CF patients are on a high calorie diet to help achieve normal growth and development and maintain good lung function. Inadequate caloric intake in CF can lead to malnutrition. Malnutrition in CF requires careful, multidisciplinary history taking, physical exam, and overall patient/family assessment. Only by determining the actual cause of the malnutrition can appropriate and safe therapies be used to treat it. Appetite stimulants, although efficacious in treating malnutrition in CF, should only be prescribed if decreased food intake secondary to inadequate appetite is the principal cause of the malnutrition and all other contributing factors have been assessed, ruled-out or treated. In this review, we attempted to summarize the use of several appetite stimulants used in CF and other diseases to improve appetite and maximize caloric intake. **Pediatr Pulmonol. 2008; 43:209–219.**

Key words: cystic fibrosis; appetite stimulants; megestrol acetate; cyproheptadine hydrochloride; dronabinol; antipsychotic drugs; antidepressants; recombinant human growth hormone; anabolic androgenic steroids.

INTRODUCTION

The fundamental nutritional goal for cystic fibrosis (CF) is to achieve normal growth and development and, once genetic potential is reached, to maintain good nutritional status throughout life. Evidence has shown that lung function is closely associated with nutritional status in CF[1–3] and that nutritional status is an independent predictor of survival.[4] Despite this knowledge, a large proportion of the CF population still is not able to achieve this nutritional goal. Epidemiological studies from the USA have revealed three times the expected prevalence of CF patients below the 10th percentile for height and weight.[5]

Good nutritional status is dependent on the consumption of adequate nutrients, which is driven by complex, inter-related factors such as physical hunger, appetite, food-related behaviors, emotions, knowledge, and beliefs. Table 1 focuses on multiple issues possibly contributing to poor appetite or poor food intake in CF. Some of these factors are directly related to CF and others are not but may be more prevalent in people with CF because of the impact of the disease or the treatments on overall well-being.

There are several phases to food intake. First, there is the gastric motility phase which is mediated by the vagus afferents. This is followed by the post absorptive phase which is mediated by the duodenal release of cholecystokinin (CCK). Other hormones that are released include ghrelin, and peptide YY3 (PYY). CCK promotes satiety and slows gastric emptying by contracting the pyloric sphincter. Ghrelin signals hunger and PYY promotes

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TABLE 1— Issues Contributing to Poor Appetite or Poor Food Intake

CF related		Can occur in people with CF	
Acute illness, pulmonary exacerbation, inflammation, increased cytokines	Poor gastric emptying and/or gastroesphageal reflux	Depression, anxiety, stress or sadness	Eating disorder or disordered eating behaviors
DIOS (distal intestinal obstructive syndrome) or constipation leading to abdominal pain and nausea	Nasal polyps which may impair taste or the ability to eat and breathe comfortably at the same time	Inflammatory bowel disease	Appetite neuro-transmitter abnormality (ghrelin, peptide Y, leptin, insulin)
Avoidance of foods mistakenly thought to be 'bad' for CF (''carbohydrates causing CF-related Diabetes'', ''fats causing abdominal pain'', ''milk/milk products causing secretions'' etc.).	Sinusitis which may be associated with pain with chewing, or altered taste	Medications (some antidepressants or attention deficit hyperactivity disorder (ADHD) medications)	Economic oraccess issues
Burden of therapies on time and energy to prepare and eat nutritious foods		Abdominal pain, bloating or other symptoms of malabsorption	

satiety by inhibiting gut motility. Thirdly, there is the metabolic phase which results in the release of glucose, insulin, and leptin. Finally, the ileal phase results in the inhibition of gastric motility by inhibiting neuropeptide Y release from the brain.[6–9]

In order to understand malnutrition in CF, each phase of this process must be considered. Diagnosing the cause of an individual's malnutrition requires careful, multidisciplinary history taking, physical exam, and overall patient/family assessment. Only by determining the actual cause of the malnutrition can appropriate and safe therapies be used to treat it. Table 2 provides a framework for this process. Issues listed in the table should be addressed thoroughly. If malnutrition persists, appetite stimulants should be considered.

Appetite stimulants, although efficacious in treating malnutrition in CF, should only be prescribed if decreased food intake secondary to inadequate appetite is the principal cause of the malnutrition and all other contributing factors have been assessed, ruled-out, or treated. For example, if depression is the principle cause of poor food intake in a person with CF, it would be appropriate to consider consulting a psychologist or a psychiatrist. It is important that physicians treating depression in CF are aware of the secondary effects of different antidepressants on appetite in order not to further exacerbate the problem. If the only therapy provided is appetite stimulants, the problem of poor appetite may be effectively reversed, but the depression is still present and untreated. Similarly, if poor GI motility is the primary cause of poor food intake, increased intakes achieved by the use of appetite stimulants may lead to the exacerbation of the GI symptoms. In this case, motility agents may be equally or more effective and the underlying problem, not just the symptoms, would be treated. Clinically, many of these issues may be inseparable and appetite stimulants may need to be prescribed in concert with other treatments, but the other issues should also receive the attention and treatment they deserve.

In this review, we attempted to summarize the use of several appetite stimulants used in CF patients and patients with other chronic diseases to improve their appetite and maximize their caloric intake.

ABBREVIATIONS

CF	cystic fibrosis
MA	megestrol acetate
CH	cyproheptadine hydrochloride
BMI	body mass index
BWG	body weight gain
APDs	antipsychotic drugs
rhGH	recombinant human growth hormone
LBM	lean body mass
AAS	anabolic androgenic steroids

MEGESTROL ACETATE (MA)

Megestrol acetate (MA) (Megace®) is a synthetic, orally active derivative of progesterone. It is widely used in treating advanced breast cancer.[10] One of the side effects of MA is appetite stimulation and weight gain.[10] The mechanism of action has not been established. It has been postulated that the effect is partly mediated by neuropeptide Y, a potent central appetite stimulant.[11] In animal models, MA stimulates its synthesis, transport, and release, which may contribute to its appetite-stimulating effect.[12] Another speculation of its mechanism of action is that it is a potent inducer of adipocyte differentiation in 3T3-L1 cells in vitro, raising the possibility that it stimulates the conversion of fibroblasts to adipocytes, thereby blocking or reversing the effect of tumor necrosis factor on lipocyte differentiation.[13,14] It has been used successfully as an appetite stimulant in adult patients with cancer and acquired immunodeficiency syndrome (AIDS).[15–22] It also improved patients' general sense of well-being.[19–21]

MA has been used in CF to treat anorexia and weight loss.[23–25] In a case report, four patients, ages 10–18.5 years, with severe CF lung disease, anorexia and weight loss received MA in an effort to stimulate their

TABLE 2— Work-Up Strategies for Malnutrition in Cystic Fibrosis

Symptoms	Information, tests and possible intervention strategies
Appetite	
Decreased food intake	Diet history, food records History of events leading to poor appetite: • Temporal onset • Symptoms at the time of onset • Emotional/social/financial coexisting issues • Behavioral issues around eating Observe mealtime interactions
Early satiety	Gastric motility study
Avoidance of high energy foods	Body satisfaction, desired body weight, eating attitudes, purging behaviors (i.e., non-compliance to enzymes to lose weight)
Absorption/digestion	
Abdominal pain, gas, bloating, frequent, foul stools, visible oil loss	72 hr fecal fat coefficient of dietary fat intake Enzyme history: • List of foods or beverages with which enzymes are not taken, • Information on when and how enzymes are taken • Reported compliance to prescribed enzymes Low intestinal pH resulting in poor enzyme bioactivity: • Good compliance to enzymes reported and observed; • Enzyme dose 1,000–2,500 IU lipase/kg/meal • Minimal response to enzyme dose adjustments in recent past • Acid suppression or acid blocker therapies may be beneficial
Stool mass palpitated	Abdominal X-ray; DIOS history
Refractory symptoms	Rule out other GI processes common in CF: bacterial overgrowth, constipation, intussusception, CF-related liver disease, and/or the co-existance of lactose intolerance, celiac disease, etc.
Metabolism	
Growth failure or unintentional weight loss	Oral glucose tolerance test to rule-out glucosuric energy losses
Increased respiratory symptoms leading to elevated energy requirements	Aggressive respiratory and physio-therapies
Use of systemic and/or inhaled corticosteroids	Linear height more affected than body weight or body mass index; bone age delay
Hyponatremia	Recurrent hyponatremia or hyponatremic dehydration

appetite and improve weight gain. Three of the four patients received gastrostomy tube feedings, and all were pancreatic insufficient. The dose was 400–800 mg daily and duration of use was 6–15 months. Appetite improved, with significant weight gain in all patients and an increase in mean weight for age percentile from <5th percentile to approximately 25th percentile after 6 months of therapy was noted. Quality of life was also shown to improve.[23] Side effects were not reported in this case report. A randomized, double-blind, placebo-controlled, crossover pilot trial of MA in 12 malnourished children with CF was conducted over a 12-week period, followed by a 12-week washout period, then the alternative treatment.[24] The age range was 21 months to 10.4 years. Six patients didn't complete the study, three for reasons unrelated to the study, two because of developing diabetes while receiving MA, and one who developed glucose intolerance while receiving the placebo. Weight Z-score, body fat, and lean body mass (LBM) increased, and pulmonary function improved in patients given MA. There was little change in linear growth during MA therapy. Side effects included glucosuria, insomnia, hyperactivity, and irritability.[24] Another randomized, double-blind, placebo-controlled study was conducted to evaluate the effects of MA on CF patients.[25] Seventeen patients age 6 years and above were enrolled in the study. MA dose used was 7.5–15 mg/kg/day. The study duration was 6 months. The treatment group had significant increase in weight-for-age Z-score and reached 100% of their ideal body weight within 3 months of initiating therapy. Weight gain included both fat and fat-free mass as measured by dual energy X-ray absorptiometry (DXA). Pulmonary function improved in the treatment group compared to the placebo group. Reversible adrenal suppression was observed in the majority of patients who received MA. Some patients suffered from insomnia and moodiness while on MA.[25] We observed adrenal suppression, diabetes and insomnia in patients treated with long term MA (unpublished data). MA was also reported to cause testicular failure in CF patients and impotence in HIV-infected patients, along with its known glucocorticoid-like activity sometimes leading to Cushing Syndrome and adrenal insufficiency.[17,26,27] A case report of osteoporosis associated with MA use in cancer patients was also documented.[28]

CYPROHEPTADINE HYDROCHLORIDE (CH)

Cyproheptadine hydrochloride (CH) (Periactin®) is a first-generation antihistamine which is both a histamine and serotonin antagonist. It is also known to have a secondary effect of appetite stimulation.[29,30] The mechanism of action is unknown but it is not due to hypoglycemic induced hyperphagia, as evidenced by normal glucose tolerance testing and normal insulin levels during use. In addition, it is not due to an increase in endogenous growth hormone (GH).[29,30] It was found to stimulate weight gain in normal, underweight adults.[31] CH was shown to be an effective appetite stimulant in two studies of asthmatic children.[29,32] It was also shown to be an effective appetite stimulant in anorexia nervosa[33] and tuberculosis.[34] However, CH was not shown to be effective in producing weight gain in advanced cancer with cachexia.[35–37] Both MA and CH were studied in HIV patients and were found to be beneficial.[38]

A 12-week, randomized, double-blind, controlled study of CH versus placebo was conducted in 18 CF patients.[39] The dose used was 4 mg QID, and the duration of the study was 3 months. Sixteen patients completed the study. Subjects in the CH group showed significant increases in weight, height, body mass index (BMI) percentiles, ideal body weight/height, weight for age Z-scores, and fat and fat-free mass versus the placebo group. There were no differences in antibiotic use or spirometric measures between the two groups. No significant side effects, except transient mild sedation, occurred in the CH group and patients' acceptance and adherence were good.[39] A follow-up study was conducted to evaluate the long-term use of CH.[40] Sixteen CF patients enrolled and 12 completed a 9-month open-label trial following the completion of the double-blind study.[40] Subjects who had changed from placebo to CH gained weight significantly over 3–6 months, and those continuing on CH generally maintained previously gained weight over the duration of the study. There were some improvements, not statistically significant, in selected spirometric measures and side effects were mild.[40] From these studies, CH seems to be safe and well-tolerated. It has a modest positive effect on weight in most subjects, and with most of the gain occurring in the first few months of use.[39,40]

DRONABINOL (Marinol®)

Dronabinol (Marinol®) is an oral form of delta-9-tetrahydrocannabinol dissolved in sesame oil in soft gelatin capsules. It is the principal psychoactive substance present in marijuana. It is utilized as an alternative to smoked marijuana for AIDS wasting syndrome and nausea following chemotherapy.[41] An important gap in the knowledge base about dronabinol has been an accurate assessment of its abuse potential.[41] The most common reasons for medicinal use of marijuana in HIV/AIDS are appetite stimulation, weight gain, sleep, relaxation, depression, nausea, vomiting, pain, and combating antiretroviral side effects.[42,43] A number of studies cite the use of marijuana for treatment of cancer-related anorexia, nausea, vomiting, pain, and mood disorders.[44,45] There is no evidence of abuse or diversion of dronabinol. There is no street market or value for dronabinol.[41] Furthermore, it doesn't provide effects that are considered desirable in a drug of abuse.[41] The onset of action is slow and gradual, its effects are dysphoric and unappealing.[41,43]

A long-term study (12 months) of dronabinol was conducted in 94 late-stage AIDS patients who previously participated in a 6-week double-blind placebo-controlled study.[46] All patients received dronabinol orally at a dose of 2.5 mg twice daily (90%) or 2.5 mg once daily (10%). The long-term use of dronabinol resulted in consistent increase in appetite with trends toward weight stabilization and modest weight gain in AIDS patients.[46,47] In addition, the data from this study suggested that it may be administered long-term in this patient population without development of tolerance to the therapeutic effect. Few patients developed adverse events which were related to the central nervous system, for example, anxiety, confusion, euphoria, and somnolence.[47]

It has been proposed to administer dronabinol to CF patients to alleviate malnutrition and help treat wasting, especially with severe disease.[48] It was utilized in 11 CF patients with severe nutritional deficiencies who had failed conventional interventions of nutritional counseling and high calorie supplement. The average age of the patients was 25.9 years (range 14–44 years), and the average weight at the start of the study was 96.6 lbs. Mean FEV_1 was 26% of predicted. Patients were treated on average for 3 months (range 1–6 months). The starting dose was 2.5 mg in all patients and maximum dose was 5 mg twice daily.[49] Patients receiving dronabinol had a significant improvement in weight during the treatment period ($P = 0.03$), with average weight at the end of the treatment period of 103.8 lbs. FEV_1 was 26.5% of predicted, which was not statistically significant. Side effects noted during the study period were euphoria, hallucinations, and lethargy; each side effect only occurred in one patient. All side effects responded to lowering the dosage. No patients stopped the medication due to side effects.[49]

In conclusion, dronabinol is a safe and effective appetite stimulant with potential effectiveness in CF.

ANTIPSYCHOTIC/ANTIDEPRESSANT AGENTS

Antipsychotic Drugs

Excessive body weight gain (BWG) is a common side effect of some typical and atypical antipsychotic drugs

(APDs).[50] Weight gain is linked to a decreased metabolic rate, increased caloric intake, and decreased physical activity.[51] It is generally believed that there are multiple mechanisms by which APDs induce weight gain, but their precise nature remains unknown. Weight gain as a drug effect may be a multifactorial process, involving serotonergic, histaminergic, and/or adrenergic neurotransmission.[51] A new generation of agents, the atypical APDs, represents an important progress in the treatment of psychotic disorders. Atypical antipsychotics achieve their therapeutic effects by modulating the activity of these neural pathways. Weight gain as a side effect may also be due to the blockade of certain receptors, for example, 5-HT_{2c}, that modulate appetite and body weight.[52] Weight gain is dependent on the specific drug and individual patient. The atypical antipsychotics vary in their propensity to cause weight change with the long-term treatment. The largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight gain that is not dose related.[53] However, clozapine and olanzapine appear to display a high propensity to induce glucose dysregulation and dyslipidemia. Insulin secretion is preserved and thus high serum insulin levels are observed; there appears to be peripheral insulin resistance, which leads to glucose intolerance and type 2 diabetes mellitus (DM).[50] Sudden BWG, insulin resistance, increased appetite, and related endocrine changes also may be involved in the development of glucose intolerance and dyslipidemia in predisposed individuals. Patients' blood glucose and lipids should be monitored before treatment and at regular intervals.[50]

The use of olanzapine in an 18-year-old female with CF and severe body dysmorphism led to a significant increase in body weight, possibly by stimulating appetite.[54] This observation led to a larger open-label trial of low dose olanzapine therapy in a group of 12 adults with CF who had previously been losing weight despite maximal conventional therapy.[54] Age range was 18–40 years, with a mean age of 21 years. Mean FEV_1 was 27.4% predicted. Eleven of the 12 subjects were pancreatic insufficient, and 7 subjects were on regular insulin therapy. Olanzapine was started at 5 mg daily (usual range in psychiatric practice is 10–20 mg daily). Ten subjects continued olanzapine for at least 6 months. In two subjects, biochemical evidence of liver dysfunction was detected shortly after starting therapy and led to discontinuation of treatment with subsequent normalization of liver function. Four subjects reported increased sleepiness which responded to adjustment of the time of dosing. Six subjects reported an increase in appetite. At baseline, mean (SD) BMI was 16.65 ($\pm$1.01). After 6 months, BMI was 18.61 ($\pm$2.01). When compared to baseline, change in BMI after 6 months of therapy was statistically significant ($P = 0.01$, Wilcoxon sign-rank test).[54]

Antidepressants

Psychological functioning has been assessed in both children and adults with CF, but the results have been variable. Some studies have reported relatively normal adjustment in older adolescent and adult CF patients.[55–61] However, other studies have suggested elevated levels of psychosocial impairment, including anxiety, depression, and eating disorders.[62–65] Most of the second group of studies were done earlier than the first group (in the 1960s until early 1990s). That might be a reflection of the poorer treatment options and the shortened life expectancy then. Overall, adults with CF report relatively healthy psychological functioning.[55] Better lung function and a strong social support system predicted better psychological functioning.[55] The prevalence of psychological and psychosocial dysfunction of people with CF is associated with worsening disease severity and lack of social support.[55,66] Antidepressants have been used, in addition to other psychosocial interventions, to treat depression in CF patients.[67]

In addition, antidepressants have been used as appetite stimulants. All antidepressants have side-effects, including appetite dysregulation. The non-adrenergic and specific serotonergic antidepressants block the 5-HT_{2C} receptor (one of the serotonin receptors). Blockage of this receptor may lead to an increase in appetite.[68] They also block the 5-HT_3 (another serotonin receptor) which is the main site of action for nausea and occasional emesis. These two symptoms are usually associated with decreased appetite and failure to gain adequate weight in patients with severe CF disease.[68]

Mirtazapine (Remeron®) is a noradrenergic and specific serotonergic antidepressant (NaSSA). It also has an antihistamine effect. Its tolerability and safety profile reflects a unique pharmacological profile. It is well tolerated and shows particular benefits over other antidepressants in terms of antianxiolytic effects, sleep improvement, and gastrointestinal side-effects. Its main side-effect is weight gain.[68]

Mirtazapine has been used as an appetite stimulant in malnourished CF patients.[69,70] The first study was a pilot study of five patients age 14–19 years with mean FEV_1 of 41.4% with growth failure. They were started on 15 mg of mirtazapine once a day. Patients were on the medication for a mean of 96 days (range 29–142 days). All subjects demonstrated an increase in weight (5.8 kg, $P < 0.01$), body fat (13.9–21.8 kg, $P < 0.01$) and an increase in weight gain velocity (-3.9 before starting treatment vs. 27.4 kg/year after treatment, $P < 0.05$). All subjects reported mild sedation, dry mouth, increased thirst and increased appetite. None of the subjects felt these symptoms justified stopping the medication.[69] The second study was a retrospective study. Six patients were enrolled. Age range was 10–17 years at the start of

therapy. Doses ranged from 15 to 45 mg once daily. Patients received an average of 14.2 months of therapy (range 8–28 months). All patients had an increase in BMI percentile for age (mean 10.3%, median 8%, and range 2–25%). Adverse effects were limited to somnolence.[70]

RECOMBINANT HUMAN GROWTH HORMONE (rhGH)

Growth hormone (rhGH) has been approved by the Food and Drug Administration for use in treating AIDS-associated wasting.[71] GH is a potent anabolic agent that has been used in the posttraumatic state to reduce nitrogen loss.[72] The nitrogen retention induced by GH is associated with increased whole-body protein synthesis and LBM as well.[72] Human GH is a single polypeptide chain composed of 191 amino acids (molecular weight 22 KD) and coded on chromosome 17.[71] Secreted by the somatotrophs of the anterior pituitary gland, GH promotes protein synthesis and fat utilization and decreases glucose oxidation.[71] GH stimulates the production of insulin-like growth factor (IGF-I) in the liver and other organs (muscle, bone, adipose tissue).[71]

The recommended dosage of rhGH is 4–6 mg administered by subcutaneous injection daily. It offers a more expensive alternative, approximately 10–15 times the cost, to appetite stimulants such as MA and dronabinol.[71,73] The adverse effects associated with rhGH therapy include mild edema and arthralgias, carpal tunnel syndrome, gynecomastia, insulin resistance, and glucose intolerance. Nonetheless, treatment has generally been well tolerated.[74,75] In children, using rhGH for long-term replacement can lead to irreversible adverse effects such as slipped capital femoral epiphysis, acromegaly, and leukemia.[71]

Previous studies have documented that patients with CF have a delay in attainment of pubertal maturation.[76] The relationship between weight gain and linear growth was done, and a poor correlation was found between the two.[77] This study concluded that nutritional supplementation alone may not be the best means for improving short stature in CF.[77] GH stimulates accrual of linear height and has been used to improve weight gain in chronic illness.[78,79]

Several studies have documented the safety and efficacy of GH in improving growth and clinical status in CF patients.[80–85] A 1 year randomized controlled trial to test the effect of GH on the clinical status of CF children was conducted.[80] Nineteen prepubertal children were recruited. The GH treatment group had significantly greater height, height velocity, weight, weight velocity, and change in lean tissue mass. There was also significant improvement in delta forced vital capacity (FVC) compared with the year before the study; respiratory muscle strength also improved. The number of hospitalizations and outpatient intravenous antibiotic courses significantly decreased.[80] A multicenter, randomized, controlled trial that included 61 prepubertal CF patients confirmed the results of this study. The study duration was 1 year.[81]

Another study evaluated the mechanism of the anabolic effect of rhGH in CF patients. It was also evaluated whether glutamine (GLN) (which has shown improvement of nitrogen balance in diseases associated with severe stress and protein wasting when supplemented orally) alone has a protein anabolic effect. It also evaluated if the combination of GLN and rhGH is more potent than either one alone.[82] Nine undernourished or short CF children were recruited. The study concluded that in children with CF (1) oral GLN may not promote protein gain in the fasting state; and (2) a short course of rhGH has a potent anabolic effect that is mediated by stimulation of protein synthesis and does not affect GLN kinetics.[82]

GH was reported to enhance nutrition and growth in CF children receiving enteral nutrition.[83] A retrospective study of GH use in pubertal CF adolescents suggested that GH safely improved height, body weight, bone mineralization, and clinical status.[84] GH was evaluated in eight adult CF patients with mild or moderate pulmonary disease. In this study, GH appears to improve weight and body composition.[85] In patients with severe pulmonary disease, GH appears to stabilize loss of weight, bone and muscle mass.[85]

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the metabolic and respiratory effects of GH in 63 CF children (bone age 8–18 years).[86] BMI was <10 and/or weight <3 percentile despite a high caloric intake ($>120\%$ RDA). Height and growth velocity as well as growth factors (IGF1, IGFBP3) increased significantly ($P < 0.05$). A significant effect on weight gain was not observed. FEV_1 both absolute and in percent predicted didn't change significantly with GH treatment. The study concluded that GH therapy had positive metabolic effects but didn't improve lung function in CF patients.[86]

ANABOLIC ANDROGENIC STEROIDS (AAS)

Since anabolic androgenic steroids (AAS) are derivatives or structural modifications of the parent steroid hormone, testosterone, they exhibit both anabolic and androgenic activities.[87] Anabolic effects are the promotion of protein synthesis, nitrogen retention, and skeletal muscle growth. Androgenic effects are the development and maintenance of primary and secondary sexual characteristics in males. In females, androgenic effects are evident as male pattern baldness, deepened voice, clitoromegaly, and growth of facial hair.[87] Oxandrolone has marked anabolic activity and few androgenic effects (ratio 10:1), in comparison with testosterone and methyl-

testosterone.[88] It is a marked contrast with other oral AAS that are metabolized extensively in the liver, oxandrolone is relatively resistant to liver biotransformation. Approximately 28% of it is excreted unchanged and unconjugated in the urine.[89] Oxandrolone is the only AAS that is US FDA approved for restitution of weight loss after severe trauma, extensive surgery, chronic infections, malnutrition due to alcoholic cirrhosis, and Duchenne's or Becker's muscular dystrophy.[87] Statistically significant improvements were reported in the areas of body composition, recovery, muscle strength, and function, and/or functional status.[87] Oxandrolone is used in the treatment of short stature due to Turner's syndrome and constitutional delay of growth and puberty.[90,91] It is used in acute catabolic disorders (e.g., burn injury and acute multiple trauma).[87] It is also used in chronic catabolic disorders, for example, moderate to severe alcoholic hepatitis, chronic obstructive pulmonary disease (COPD), and Crohn's disease.[87] It has been used also in wasting associated with HIV/AIDS.[87] Adverse effects include hepatic dysfunction (increased transaminase levels), androgenic effects (alopecia, hirsutism, deep voice, and clitoromegaly in girls and women).[87] It has not been studied in CF patients.

Prednisone has been studied in CF patients with mild-moderate pulmonary disease to assess its effect on the pulmonary inflammatory process.[92] The study was a 4-year, double-blind, placebo-controlled trial of alternate-day prednisone (2 mg/kg) in 45 CF patients. The patients in the prednisone group showed better growth and pulmonary function and less morbidity compared with those in the placebo group. No complications were reported. Because of this observation, the United States Cystic Fibrosis Foundation sponsored a multicenter, double-blind, placebo-controlled trial of alternate-day prednisone at a dose of 2 mg/kg (high dose), 1 mg/kg (low-dose), or placebo every other day for 4 years. Two hundred eighty five patients from 15 CF centers were enrolled in the study from 1986 to 1987. An interim safety analysis was done with mean duration in the study of 33.9 months for the high-dose, 35.3 months for the low-dose, and 36.8 months for the placebo groups.[93] This analysis revealed increased frequency of cataracts, growth retardation, and glucose abnormalities among patients in the high-dose group.

In view of these results, it was recommended by the study ombudsman and a special advisory panel that the study drug be discontinued for all patients in the high-dose prednisone group.[93] At the end of the study, there was significant improvement in the 1 mg group compared to placebo in FVC ($P < 0.025$) in patients colonized with Pseudomonas aeruginosa at baseline.[94] In addition, there was significant improvement in predicted forced expiratory volume in 1 sec (FEV_1) in the 1 mg/kg group compared to placebo ($P < 0.02$) and reduction in serum IgG concentrations (1 mg/kg vs. placebo, $P < 0.007$; 2 mg/kg vs. placebo, $P < 0.003$). From 6 months onward, height Z-scores fell in the 2 mg/kg group compared to placebo ($P < 0.001$). For the 1 mg/kg group, height Z-scores were lower at 24 months. An excess of abnormalities in glucose metabolism was seen in the 2 mg/kg group compared with the placebo group ($P < 0.005$).[94]

An evaluation of growth pattern, 6–7 years after prednisone was discontinued in the previous study was done retrospectively, through data collected from the CF Foundation Patient Registry. The findings indicate that growth suppression induced by long-term alternate-day prednisone therapy was long-lasting in male children with CF. The impact was particularly pronounced when prednisone was taken prior to adolescence, in which case final adult height appeared to be affected.[95]

Even though oxandrolone seems to be effective in treating wasting and catabolic disorders in different chronic disorders, long-term use of prednisone had the opposite effect on growth in CF.

DISCUSSION

In view of the burden and demands on CF patient to achieve normal growth and development, appetite stimulants could be offered to help increase caloric intake. A list of appetite stimulants discussed in this review is summarized in Table 3. Several factors can lead to poor appetite and food intake in CF patients. Some of these factors are directly related to CF and others may be more prevalent in CF. Appetite stimulants should be used only after all other causes of weight loss and growth failure have been excluded. They should be limited to patients in whom conventional measures fail. Choice of appetite stimulants should be made according to physician, and CF care team experience, patient's age, severity of CF disease and known side effects. In addition, the choice of appetite stimulant should be discussed with the patient/family prior to starting treatment. Side effects of the appetite stimulant of choice should be monitored closely. An algorithm of work up and intervention for CF patients at nutritional risk is summarized in Table 4.

It has been documented that CF patients have demonstrated an overall protein catabolism, even in non-acutely ill subjects.[96–98] Negative protein balance may contribute to increased morbidity and mortality in CF by decreasing body mass, and possibly by worsening immune function.[99] An earlier study illustrated that reversal of protein catabolism resulted in stabilization of pulmonary function and decreased hospitalization rate.[100] Chronic inflammation and protein catabolism are linked to high levels of cytokines, particularly TNF-α in CF patients.[98,101,102] In one study of GH treatment of malnourished CF subjects concluded that treatment with this agent resulted in marked decrease in TNF-α levels.[98] The authors speculated that

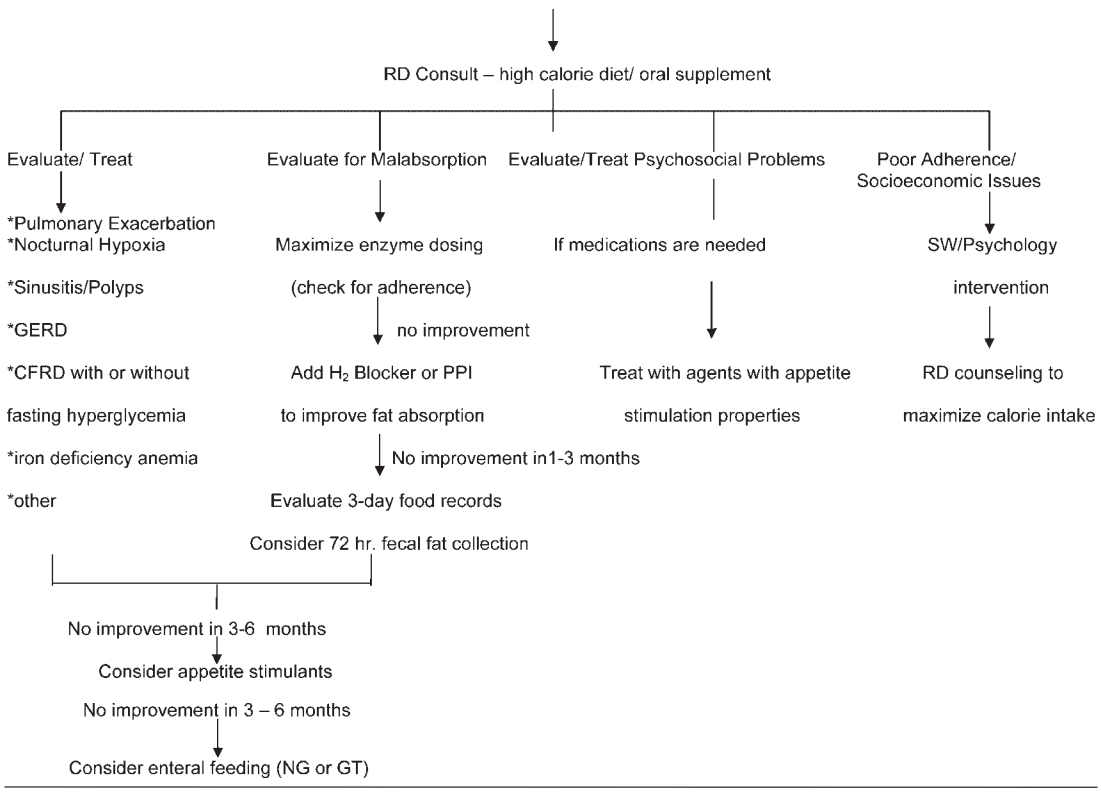
TABLE 3— Summary of Appetite Stimulants in CF

Drug	Dosage	Side effects
Megestrol acetate (MA)	400–800 mg/day or 7.5–15 mg/kg/day orally	Glucosuria, insomnia hyperactivity, irritability, reversible adrenal suppression
Cyproheptadine hydrochloride (CH)	4 mg BID–QID or 0.5 mg/kg/day orally	Transient mild sedation
Dronabinal (Marinol®)	2.5 mg qd–5 mg BID orally	Anxiety, confusion, euphoria, somnolence
Antipsychotic		
Olanzapine	5–20 mg qd orally	Liver dysfunction, sleepiness, hyperglycemia
Risperidone	0.5–5 mg qd orally	Glucose dysregulation, dyslipidemia
Antidepressents		
Mirtazapine (Remeron®)	15–45 mg qd orally	Mild sedation, dry mouth, somnolence
Recombinant human growth hormone (rhGH)	4–6 mg qd SC injection	Mild edema, arthralgia, carpal tunnel syndrome, gynecomastia, insulin resistance, glucose intolerance. In children, slipped capital femoral epiphysis, acromegaly, leukemia
Anabolic androgenic steroids (AAS)		
Oxandrolone	0.1 mg/kg/day BID, orally	Hepatic dysfunction, androgenic effects in females (alopecia, hirsutism, deep voice, clitoromegaly), development of primary and secondary sexual features in males. Not studied in CF

this may have been due to improved clinical status in this treated group.

Appetite stimulants can be used prior to resorting to invasive means to treat CF patients at nutritional risk. However, the use of appetite stimulants and their benefits in CF have been based on case reports and small studies. More research is needed in this area to establish the effect of improving nutritional status especially by adding appetite stimulants, on the proinflammatory markers (cytokines, TNF-α and others) and CF lung disease.

TABLE 4— Algorithm for Cystic Fibrosis Patients at Nutritional Risk (BMI Percentile ≤25% or Poor Weight Gain for 3 Months)



MA, CH, Dronabinol, and antidepressants have immunomodulatory effects. It would be interesting to study the effects of these agents on the inflammatory markers as well as appetite stimulation in large long terms studies. Larger comparative studies with different appetite stimulants in CF especially of longer durations and appropriately powered would be beneficial.

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