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The Use of Appetite Stimulants and Anabolic Agents in Hemodialysis Patients

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Indices of malnutrition related to morbidity and mortality in the hemodialysis population have been well-established. Many steps are taken to prevent malnutrition and the increased morbidity and mortality risk in this population. However, data is limited regarding

the benefit of the reversal of malnutrition. Several nonrandomized studies show decreased mortality with the provision of nutritional supplementation to these patients (1). The cause of protein-calorie malnutrition is often multifactorial and the provision of increased nutrients may not be the only solution.

This article reviews the pharmacological approaches to increase appetite and weight gain in the hemodialysis population.

It includes information about appetite stimulants and anabolic agents used in other patient populations that may have limited or no data regarding their use in the hemodialysis population. Table 1 summarizes the nutritional benefits, dosage and administration information, and side effects of these pharmacologic approaches. Several appetite stimulants have demonstrated varying results in

Continued on page 3

Table 1. Appetite Stimulants and Anabolic Agents

Name of Drug	Description	Nutritional Benefits	Dosage and Administration	Potential Side Effects	Precautions
Megestrol Acetate (Megace)	Oral derivative of the steroid progesterone	Increased oral intake and weight gain (mostly fat, not lean body mass), increased albumin	Low dose-40-160 mg/d up to 400 mg/d Available in 40 mg/mL suspension and 20 and 40 mg tablets	Fluid retention, diarrhea, irregular menses, hypervolemia, encephalopathy, depression, impotence	Diabetics-monitor carefully. DVT risk in immobile pts. Monitor for adrenal suppression.
Cyproheptadine (Periactin)	Antihistaminic and antiserotonergic agent	Increased appetite is a side effect of this drug	4 mg tablets. In adult HD pts, give 1 tablet at bedtime to alleviate sedating effect during the day	Increased appetite, Central Nervous System depression	Overdosage in kids; cautious use in patients with asthma, hyperthyroidism, CVD and HTN
Dronabinol (Marinol)	Synthetic Delta-9-Tetrahydrocannabinol which is a naturally occurring component of cannabis	Treatment of anorexia associated with wt. loss in AIDS; for N/V from chemotherapy after conventional treatment failure	Round, soft gelatin capsules containing either 2.5mg, 5 mg, or 10 mg dronabinol. 2.5 mg before lunch and dinner average dose	Feeling high, dizziness, confusion, somnolence	Allergy to sesame oil. Not studied in peds. Do not use with history of CVD, substance abuse, psychological disease
Growth Hormone (recombinant human growth hormone)	Most abundant hormone produced by the pituitary, responsible for tissue growth and repair	Increased growth velocity in children. Possibly decreased atherogenesis in children	.5-1.0 IU/kg/week in pediatric hemodialysis pts. 0.05IU/kg/day in adults. SubQ or IM injection	Carpal tunnel syndrome, gynecomastia	Caution in patients with diabetes, infection, malignancy, or steroid use.
Testosterone (Depo-Testosterone)	Androgenic Hormone	Increased lean body mass, weight gain	Available in 100 mg/mL and 200 mg/mL solutions for IM injection ONLY. 50-400 mg q2-4 wks.	Edema, gynecomastia, hirsutism, nausea, jaundice, nitrogen and electrolyte retention, hypercalcemia	Allergy to cottonseed oil. Can cause growth retardation in children. Monitor for hypercalcemia
Oxandrolone (Oxandrin)	Anabolic steroid that is a synthetic derivative of testosterone	Weight gain after weight loss due to extensive surgery, trauma; offset catabolism due to steroid use	2.5 mg tablets 2-4 times daily	Electrolyte retention, hepatotoxicity, cholestatic jaundice, hypercalcemia	Increased prothrombin time, decreased clotting factors. Monitor for hypercalcemia

The Use of Appetite Stimulants ...

continued from page 1

improving nutritional status: megestrol acetate (Megace), cyproheptadine (Periactin), and dronabinol (Marinol).

Megestrol acetate is an oral derivative of the steroid progesterone. It has been used successfully in cancer and HIV patients to improve appetite and promote weight gain. It has been shown to decrease interleukin-6 and tumor necrosis factor- α , which negatively affect nutritional status by leading to increased muscle wasting, inhibited albumin synthesis, and decreased food intake (2). Several studies and case reports have examined its use in dialysis patients. Varying low-to-moderate doses of 40-320 mg/day improved appetite, increased serum albumin levels (although not statistically significantly), and promoted weight gain (3-5). These studies reported no negative side effects with this dosage. However, there are reported side effects in other patient groups with higher doses: fluid retention, diarrhea, irregular menses, hypervolemia, encephalopathy, depression, impotence, rash, adrenal suppression, and hyperglycemia (6-8). Caution should be used in patients with histories of deep vein thromboses (DVT) or immobile patients at higher risk for DVT because megestrol acetate may lead to a hypercoagulability state (9). Megestrol acetate has been shown to increase fat mass, but not lean body mass (6). Weight, blood pressure, electrolytes, and interdialytic weight gain (IDWG) should be monitored in hemodialysis patients receiving this drug. Glycemic control should be monitored in diabetics receiving megestrol acetate.

Cyproheptadine is an oral antihistamine with a side effect of appetite stimulation. Data is inconclusive regarding its effect on nutritional parameters (10, 11). There are no randomized controlled trials demonstrating the effect of cyproheptadine on nutritional parameters in hemodialysis patients. However, it has been used safely in adult hemodialysis patients with varying results. It should be used cautiously in children. One case report revealed toxic psychosis in a child on hemodialysis receiving cyproheptadine (12).

Dronabinol is a cannabinoid derivative that stimulates appetite and acts as an antiemetic.

Other properties include analgesic, muscle relaxation, immunosuppression, anti-inflammation, antihistamine, mood elevation and sedation (13). The major negative side effect of dronabinol, however, is that it impairs cognition (14). Dronabinol also caused pressor, renal, and mesenteric vasoconstriction and hindquarter vasodilation in Sprague-Dawley rats (15). There are no studies examining cannabinoid use in hemodialysis patients. Dronabinol is not recommended for use in patients with a history of substance abuse, depression or cardiovascular disease.

Other approaches to improved nutritional status in hemodialysis patients have focused on restoring lean body mass. Anabolic agents such as growth hormone, testosterone and oxandrolone are reviewed below.

The anabolic effects of growth hormone on stature have been studied in children on hemodialysis. Pediatric dialysis patients who have received recombinant human growth hormone (rhGH) have a higher growth velocity and are more likely to achieve near-normal adult height. Growth hormone has been most effective on final height if given in the early stages of chronic renal failure in children (16, 17). Growth hormone may also have a role in the prevention of atherosclerosis in children (18).

Growth hormone has been studied in the malnourished adult hemodialysis patient with less promising outcomes. Nutritional and anthropometric measures have not been shown to improve with rhGH, whereas bone turnover was shown to increase with a reduction in bone mineral density at the lumbar spine. Total body fat decreases with rhGH, but lean body mass has not been shown to increase. Phagocytic activity of polymorphonuclear leukocytes increased with rhGH, which is relevant in patient populations at risk of infections (19-21). When given to elderly hemodialysis patients, rhGH decreased triglyceride levels, had no effect on blood pressure, and increased bone metabolism (22). Insulin-like growth factor (rhIGF-I) is the major component of rhGH responsible for its actions. However, rhIGF-I given alone has negative side effects: jaw pain, nausea, hypoglycemia, impaired

cognition, and cardiac arrhythmias (23). It can adversely affect glycemic control in diabetics.

The anabolic agent testosterone has been used widely in hemodialysis patients to treat impotence. Improvements in nutritional and anthropometric measures have been observed with its use in geriatric patients: anabolism and weight gain. However, patients receiving testosterone experience androgenic side effects (24). Oxandrolone is an oral anabolic agent approved for the treatment of weight loss. It increases anabolism greater than testosterone without the androgenic side effects. Data is limited regarding its use in hemodialysis patients (25, 26).

Malnutrition in hemodialysis patients remains a complex problem. Treating malnutrition must focus on the multifactorial causes of involuntary weight loss and hypoalbuminemia. There are pharmacological treatments to increase appetite and promote anabolism, however, the research elucidating their benefits and side effects is limited.

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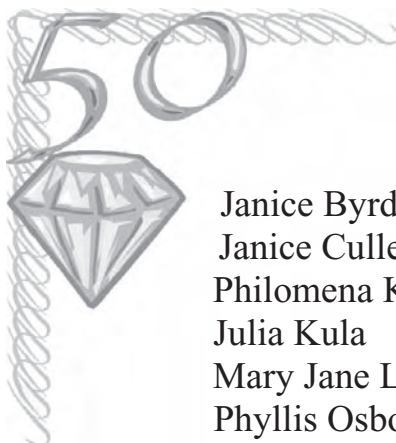
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Continued on page 4

The Use of Appetite Stimulants ...

continued from page 3

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