# Agents Used as Appetite Stimulants
# Drug Class Review

**Dronabinol**
**Megestrol**
**Oxandrolone**

**Final Report**
**March 2014**

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## Executive Summary

**Introduction:** Three appetite stimulant agents are currently approved for use in the US: megestrol, oxandrolone and dronabinol. Megestrol is a progesterone available as an oral tablet or suspension indicated in the treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS. Oxandrolone is an oral anabolic steroid indicated as an adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections or severe trauma. Dronabinol is a cannabinoid available in an oral capsule indicated in the treatment of AIDS-related anorexia.

Decreased appetite and weight loss may occur as a result of any number of conditions, including: age, psychological disorders, cancer, gastrointestinal disorders, other chronic diseases and chronic infections and as a side effect of some medications. Not only do decreased appetite and weight loss negatively impact a patient's quality of life, but they also increase morbidity and mortality in patients. Unintentional weight loss can be serious in infections and chronic disorders as the body mobilizes protein stored in the muscle to fuel the immune system or other organ systems resulting in profound loss of muscle mass and weakness.

**Clinical Efficacy:** The comparative clinical evidence evaluating the appetite stimulants in patients with decreased appetite and weight loss is limited. Two systematic reviews were identified for evaluation of the agents. Overall, the limited evidence suggests megestrol is an effective treatment option for anorexia-cachexia syndrome associated with any etiology. There is not enough comparative evidence to determine whether the efficacy varies between megestrol, oxandrolone and dronabinol therapies. Some evidence suggests dronabinol decreases nausea and increases appetite but has only an insignificant effect on weight gain while megestrol is effective in increasing body weight but the weight gain appears to be mostly in the form of fat. Oxandrolone is effective in increasing both body weight and lean body mass but its use is limited by side effects.

**Adverse Drug Reactions:** Adverse events vary between the agents. The most common adverse events reported with dronabinol use are CNS effects, including dizziness, drowsiness, confusion, hallucinations and feelings of depression. The most common adverse effects reported with megestrol use include gastrointestinal upset, trouble sleeping, mood changes and testicular failure. More serious adverse events include inducing/exacerbating diabetes mellitus, edema and thromboembolic events. The most common adverse effects reported with oxandrolone use include acne, changes in sexual desire, deepening of the voice, unusual hair growth, menstrual irregularities, mental or mood changes and gastrointestinal upset. Serious adverse effects associated with oxandrolone use include liver damage and an increase in serum lipids.

**Summary:** Overall, the appetite stimulants may be used in the treatment of anorexia-cachexia syndrome associated with any etiology. Clinical evidence is limited and adverse effects vary between the agents. Selection of an agent should be based on patient specific and disease specific characteristics, including etiology of the reduced appetite and weight loss, gender and age of the patient, patient history and concurrent medication therapies.

## Introduction

Appetite stimulants are a group of agents used in the treatment of decreased appetite and troublesome weight loss which may occur with age, psychological disorders, cancer, gastrointestinal disorders, other chronic diseases and chronic infections and as a side effect of some medications.[1] Agents used as appetite stimulants include the off-label use of some antidepressants, antihistamines and anticonvulsants, and use of various corticosteroids, cannabinoids, anabolic steroid agents and megestrol.[2, 3] This review will focus on the three agents labeled by the Food and Drug Administration (FDA) as appetite stimulants: dronabinol, megestrol and oxandrolone. Dronabinol is available as an oral capsule, oxandrolone is available as an oral tablet and megestrol is available as both an oral tablet and an oral suspension.[2, 3] See Table 1 for a list of agents used as appetite stimulants and Table 2 for a summary of the three agents reviewed in this document.

*Disease Overview*

Decreased appetite and weight loss may occur as a result of any number of conditions, including: age, psychological disorders (depression, stress, anxiety), cancer, gastrointestinal disorders (gastroesophageal reflux disease, peptic ulcer disease, ulcerative colitis), chronic diseases (chronic obstructive pulmonary disease, cystic fibrosis, Parkinson's disease), chronic infections (human immunodeficiency virus infection, acquired immune deficiency syndrome (HIV/AIDS)) and some medications (chemotherapy, amphetamines, laxatives).[1] Not only do decreased appetite and weight loss negatively impact a patient's quality of life but they also increase morbidity and mortality in patients. Unintentional weight loss (UIWL) can be serious in infection and chronic disorders as the body mobilizes protein stored in the muscle to fuel the immune system or other organ systems resulting in profound loss of muscle mass and weakness.[4, 5]

UIWL is defined as a 5% loss of actual body weight in a single month or a 10% loss during a six month period.[4, 5] UIWL may lead to a number of complications including anemia, immune deficiency, postoperative complications, a decline in activities of daily living, pressure ulcers, and falls.[5] In general, if the weight loss is not at a dangerous level and the patient is not bothered by the symptoms, no treatment is required.[1] If, however, appetite and weight loss are concerning, education should be provided about nutrition and the importance of focusing on pleasant food preferences and eating experiences. Pharmacological and non-pharmacologic appetite stimulants may also be used to treat the lack of appetite. Pharmacotherapy treatment options include some antidepressants, antihistamines and anticonvulsants, and use of various corticosteroids, cannabinoids, anabolic steroids and megestrol. See Table 1 for a summary of the agents used as appetite stimulants. Three agents have FDA labeled indications as an appetite stimulant: megestrol, oxandrolone and dronabinol. Megestrol is a progesterone indicated in the treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS. Oxandrolone is an oral anabolic steroid indicated as an adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections or severe trauma. And dronabinol is a cannabinoid indicated in the treatment of AIDS-related anorexia. Table 2 provides a summary of the three US labeled appetite stimulants agents.

## Table 1. Agents Used as Appetite Stimulants[1-3, 6]

| Therapeutic Class | Agents | Labeled Indications | Unlabeled Indications |
|---|---|---|---|
| Antidepressants | *Mirtazapine (Remeron)*<br>*Amitriptyline (Elavil)* | Treatment of depression | Alzheimer's dementia-related depression; post-traumatic stress disorder (PTSD); Analgesic for certain chronic and neuropathic pain; prophylaxis against migraine headaches; appetite stimulant |
| Anticonvulsants | *Gabapentin (Neurontin)*<br>*Pregabalin (Lyrica)* | Adjunct for treatment of partial seizures; management of postherpetic neuralgia (PHN) in adults; neuropathic pain; fibromyalgia | Diabetic peripheral neuropathy, postoperative pain (adjunct), restless legs syndrome (RLS), vasomotor symptoms |
| Antihistamines | *Cyproheptadine* | Perennial and seasonal allergic rhinitis and other allergic symptoms including urticaria | Migraine headache prophylaxis, pruritus, serotonin syndrome, spasticity associated with spinal cord damage, weight gain |
| Antipsychotics | *Olanzapine (Zyprexa)*<br>*Quetiapine (Seroquel)* | Treatment of schizophrenia or mania episodes associated with bipolar disorder | Treatment of psychosis/schizophrenia in children; chronic pain; prevention of chemotherapy-associated delayed nausea or vomiting; psychosis/agitation related to Alzheimer's dementia; acute treatment of delirium |
| Anabolic steroids | *Oxandrolone (Oxandrin)*<br>*Testosterone* | Oxandrolone: Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma<br>Testosterone: Androgen replacement therapy in the treatment of delayed male puberty; male hypogonadism; inoperable metastatic female breast cancer | Testosterone: Promote weight gain |
| Cannabinoids | *Dronabinol (Marinol)*<br>*Nabilone (Cesamet)* | Dronabinol: Chemotherapy-associated nausea and vomiting refractory to other antiemetic(s); AIDS-related anorexia<br>Nabilone: Treatment of refractory nausea and vomiting associated with cancer chemotherapy | Dronabinol: Cancer-related anorexia |
| Corticosteroids | *Dexamethasone*<br>*Prednisone*<br>*Hydrocortisone* | Primarily as an anti-inflammatory or immunosuppressant agent in the treatment of a variety of diseases, management of cerebral edema, chronic swelling, as a diagnostic agent, (Cushing's syndrome), antiemetic | Prevention and treatment of acute mountain sickness and high altitude cerebral edema; accelerate fetal lung maturation in patients with preterm labor |
| Pregnene steroids | *Megestrol*<br>*Medroxyprogesterone* | Megestrol: Tablet: Palliative treatment of advanced breast and endometrial carcinoma<br>Suspension: Treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS<br>Medroxyprogesterone: Secondary amenorrhea or abnormal uterine bleeding due to hormonal imbalance; reduction of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving conjugated estrogens; prevention of pregnancy; management of endometriosis-associated pain; adjunctive therapy and palliative treatment of recurrent and metastatic endometrial carcinoma | Medroxyprogesterone: Treatment of low-grade endometrial stromal sarcoma; treatment of paraphilia/hypersexuality |

## Table 2. Comparison of the Labeled Appetite Stimulant Agents[2, 3]

| Agent | Dosage Form | Indications | Dosing Recommendations | Generic Availability |
|---|---|---|---|---|
| **Dronabinol (Marinol®)** | Oral capsule: 2.5 mg, 5 mg, 10 mg | Chemotherapy-associated nausea and vomiting refractory to other antiemetic(s); AIDS-related anorexia<br><br>Unlabeled: Cancer-related anorexia | Antiemetic: 5 mg/m$^2$ 1-3 hours before chemotherapy, then every 2-4 hours for a total of 4-6 doses/day; maximum 15 mg/m$^2$ if needed<br><br>Appetite stimulant (AIDS-related): 2.5 mg twice daily; maximum of 20 mg/day<br><br>Pediatric<br>Antiemetic: Refer to adult dosing | Yes |
| **Megestrol (Megace®)** | Oral suspension: 40 mg/mL; 400 mg/10 mL; 625 mg/5 mL [contains alcohol, sodium benzoate; lemon-lime flavor]<br><br>Oral tablet: 20 mg, 40 mg | Tablet: Palliative treatment of advanced breast and endometrial carcinoma<br><br>Suspension: Treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS | Breast carcinoma (females): 40 mg 4 times/day (refer to individual protocols)<br><br>Endometrial carcinoma: 40-320 mg/day in divided doses (refer to individual protocols); use for 2 months to determine efficacy; maximum doses used have been up to 800 mg/day<br><br>HIV-related cachexia (males/females): 400-800 mg/day | Yes |
| **Oxandrolone (Oxandrin®)** | Oral tablet: 2.5 mg, 10 mg | Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, severe trauma, and in patients without definite pathophysiologic reasons; to offset protein catabolism with prolonged corticosteroid administration; relief of bone pain associated with osteoporosis | 2.5-20 mg in divided doses 2-4 times daily based on individual response; therapy of 2-4 weeks and repeated intermittently as needed<br><br>Geriatric<br>5 mg twice daily<br><br>Pediatric<br>Total daily dose: ≤0.1 mg/kg | Yes |

**Mechanisms of Action**[7-12]

All of the agents included in this review work via different mechanisms of action but are suitable treatment options as appetite stimulants in patients with reduced appetite and weight loss of any etiology.

Dronabinol: The exact mechanism of action of dronabinol is unknown; although, the antiemetic activity is thought to be due to its effect on cannabinoid receptors within the central nervous system. Dronabinol may also inhibit activity in the "vomiting center" in the brainstem and suppress the synthesis and activity of prostaglandins.

Megestrol: The stimulation of appetite by megestrol may occur as a result of an antagonizing effect on catabolic cytokines. Megestrol is a synthetic progestin with antiestrogenic properties. Overall, megestrol disrupts the normal estrogen cycle and results in a lower luteinizing hormone (LH) titer. Megestrol also has antineoplastic properties via antileutenizing effects which are mediated through the pituitary gland.

Oxandrolone: Oxandrolone is a synthetic testosterone derivative with similar androgenic and anabolic actions. Anabolic steroids, like testosterone and oxandrolone, promote protein anabolism and reverse catabolic processes resulting in appetite stimulation by stimulating the release of testosterone in a way that closely mimics normal physiologic testosterone levels.

## Table 3. Pharmacokinetic and Pharmacodynamic Properties of the Appetite Stimulants[2, 3]

| Agents | Therapeutic Class | Action | Absorption | Half-life | Metabolism and Excretion |
|---|---|---|---|---|---|
| **Dronabinol** | Cannabinoid | Onset of action: ~1 hour<br><br>Peak effect: 2-4 hours<br><br>Duration: 24 hours<br><br>Time to peak: 0.5-4 hours | Absorption: 90% to 95%; 10% to 20% of dose gets into systemic circulation | Dronabinol: 25-36 hours (terminal)<br><br>Dronabinol metabolites: 44-59 hours | Hepatic to at least 50 metabolites, some of which are active; 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) is the major metabolite; extensive first-pass effect<br><br>Protein binding: 97% to 99%<br><br>Excretion: Feces (50% as unconjugated metabolites, 5% as unchanged drug); urine (10% to 15% as acid metabolites and conjugates) |
| **Megestrol** | Progestin | Time to peak: 1-3 hours | Well absorbed orally | 13-105 hours | Hepatic (to free steroids and glucuronide conjugates)<br><br>Excretion: Urine (57% to 78%; 5% to 8% as metabolites); feces (8% to 30%) |
| **Oxandrolone** | Anabolic steroid | Time to peak: 1 hours | Well absorbed after oral administration | 10-13 hours | Partially metabolized via sulfation to 17-epioxandrolone; other metabolites<br><br>Protein Binding: 95%<br><br>Excreted principally in urine as unchanged and unconjugated oxandrolone (28%) |

## Methods

A literature search was conducted to identify articles addressing clinical safety or efficacy of the appetite stimulant agents, searching the MEDLINE database (1993 – 2014), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English evaluating efficacy of the agents in any etiology are included. Trials of monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded.[7-32]

## Clinical Efficacy

The comparative evidence evaluating the appetite stimulants in patients with decreased appetite and weight loss is limited. Overall, two systematic reviews were identified for evaluation of the agents. Lopez et al[25] published a systematic review of twenty-six studies comparing megestrol to placebo, corticosteroids, dronabinol and/or nandrolone in 2004. A total of 3,887 patients with cancer or AIDS were included in the evaluation. In patients with cancer, megestrol increased appetite and improved quality of life when compared to placebo. In patients with AIDS, megestrol therapy produced higher rates of weight gain when compared to placebo. Two studies comparing megestrol to dronabinol were included in the analysis. According to the limited data, megestrol may be more effective in improving appetite in patients with either AIDS or cancer. No differences in efficacy were reported between low dose (<800 mg/day) and high dose (>800 mg/day) megestrol treatment groups. The most frequent adverse effects reported in across the trials included impotence in men, deep vein thrombosis and gastrointestinal intolerance. Edema of the lower limbs was the only adverse event which was reported more frequently in the megestrol treatment group compared to placebo. No other differences in rate of adverse events were reported between active treatment and placebo groups.

In 2013, Garcia et al[26] completed an update to an earlier Cochrane review (2005) of megestrol in the treatment of anorexia-cachexia syndrome. In total, 35 trials comprising 3,963 patients were included in the analysis. Sixteen trials compared megestrol to placebo, ten trials compared different doses of megestrol and seven trials compared megestrol to other drug treatments. Of the active comparison trials, two trials compared megestrol to dronabinol and two trials compared megestrol to oxandrolone. Compared to placebo, treatment with megestrol was associated with increased rates of appetite improvement and weight gain in patients with cancer, AIDS and other underlying conditions. No differences in efficacy were reported between megestrol treatment groups and either dronabinol treatment groups or oxandrolone treatment groups. Overall, adverse events were reported more frequently in the megestrol treatment group compared to placebo including edema, thromboembolic events and deaths.

Overall, this limited comparative clinical evidence of the appetite stimulant agents suggests megestrol is an effective treatment option for anorexia-cachexia syndrome associated with any etiology. There is not enough comparative evidence to determine whether the efficacy varies between megestrol, oxandrolone and dronabinol treatment groups. The evidence does

demonstrate increased rates of adverse events with megestrol when compared to placebo, especially edema and thromboembolic events.

## Adverse Drug Reactions[1-3, 7, 9, 10, 33]

Rate and extent of adverse events vary between the three appetite stimulants. Selection of an agent should be based on patient specific and disease specific characteristics, including etiology of the reduced appetite and weight loss, gender and age of the patient, patient history and concurrent medication therapies.

Dronabinol. The most common adverse events reported with dronabinol use are related to central nervous system effects, including anxiety, dizziness, drowsiness, confusion, hallucinations and feelings of depression. Limited clinical data suggest dronabinol decreases nausea and increases appetite but only an insignificant weight gain or, in some cases, a weight loss may occur.

Megestrol. The most common adverse effects reported with megestrol use include gastrointestinal upset (diarrhea, gas), trouble sleeping, mood changes and testicular failure. Use in males is not highly recommended. More serious adverse events reported with megestrol use include inducing/exacerbating diabetes mellitus, edema, thromboembolic events and Cushing's syndrome or adrenal insufficiency if discontinued abruptly. The clinical data suggest megestrol is effective in increasing body weight but the weight gain appears to be mostly in the form of fat, which can contribute to the adverse effects of the agent.

Oxandrolone. The most common adverse effects reported with oxandrolone use are related to testosterone-like effects and include acne, changes in sexual desire, deepening of the voice, unusual hair growth, menstrual irregularities, mental or mood changes and gastrointestinal upset (nausea , vomiting). Use in females is not highly recommended. More serious adverse effects associated with oxandrolone use include liver damage and an increase in serum lipids. The clinical data suggest oxandrolone is effective in increasing body weight and lean body mass; although, some evidence suggests the weight gain may be in the form of fat.

## Summary

Three appetite stimulant agents are currently approved for use in the US: megestrol, oxandrolone and dronabinol. Megestrol is a progesterone available as an oral tablet or suspension indicated in the treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS. Oxandrolone is an oral anabolic steroid indicated as an adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections or severe trauma. Dronabinol is a cannabinoid available in an oral capsule indicated in the treatment of AIDS-related anorexia. The appetite stimulants promote appetite and weight gain in patients with chronic diseases and infections.

The comparative clinical evidence evaluating the appetite stimulants in patients with decreased appetite and weight loss is limited. Two systematic reviews were identified for

evaluation of the agents. Overall, the limited evidence suggests megestrol is an effective treatment option for anorexia-cachexia syndrome associated with any etiology. There is not enough comparative evidence to determine whether the efficacy varies between megestrol, oxandrolone and dronabinol therapies. Some evidence suggests dronabinol decreases nausea and increases appetite but has only an insignificant effect on weight gain while megestrol is effective in increasing body weight but the weight gain appears to be mostly in the form of fat. Oxandrolone is effective in increasing both body weight and lean body mass but the use is limited by side effects.

Adverse events vary between the agents. The most common adverse events reported with dronabinol use are CNS effects, including dizziness, drowsiness, confusion, hallucinations and feelings of depression. The most common adverse effects reported with megestrol use include gastrointestinal upset, trouble sleeping, mood changes and testicular failure. More serious adverse events include inducing/exacerbating diabetes mellitus, edema and thromboembolic events. The most common adverse effects reported with oxandrolone use include acne, changes in sexual desire, deepening of the voice, unusual hair growth, menstrual irregularities, mental or mood changes and gastrointestinal upset. Serious adverse effects associated with oxandrolone use include liver damage and an increase in serum lipids.

Overall, the appetite stimulants may be used in the treatment of anorexia-cachexia syndrome associated with any etiology. Clinical evidence is limited and adverse effects vary between the agents. Selection of an agent should be based on patient specific and disease specific characteristics, including etiology of the reduced appetite and weight loss, gender and age of the patient, patient history and concurrent medication therapies.

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