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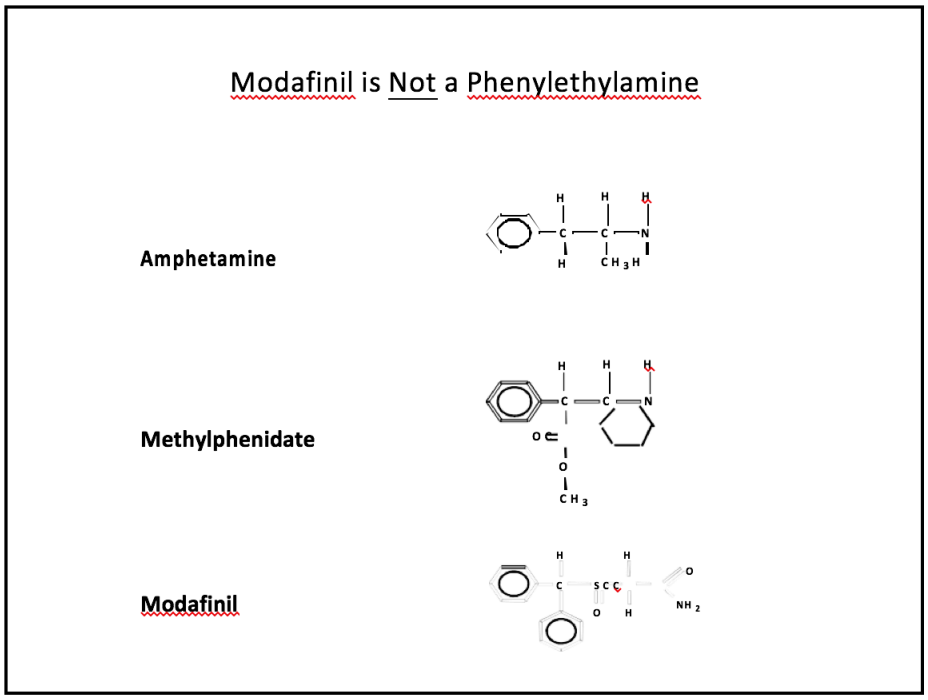
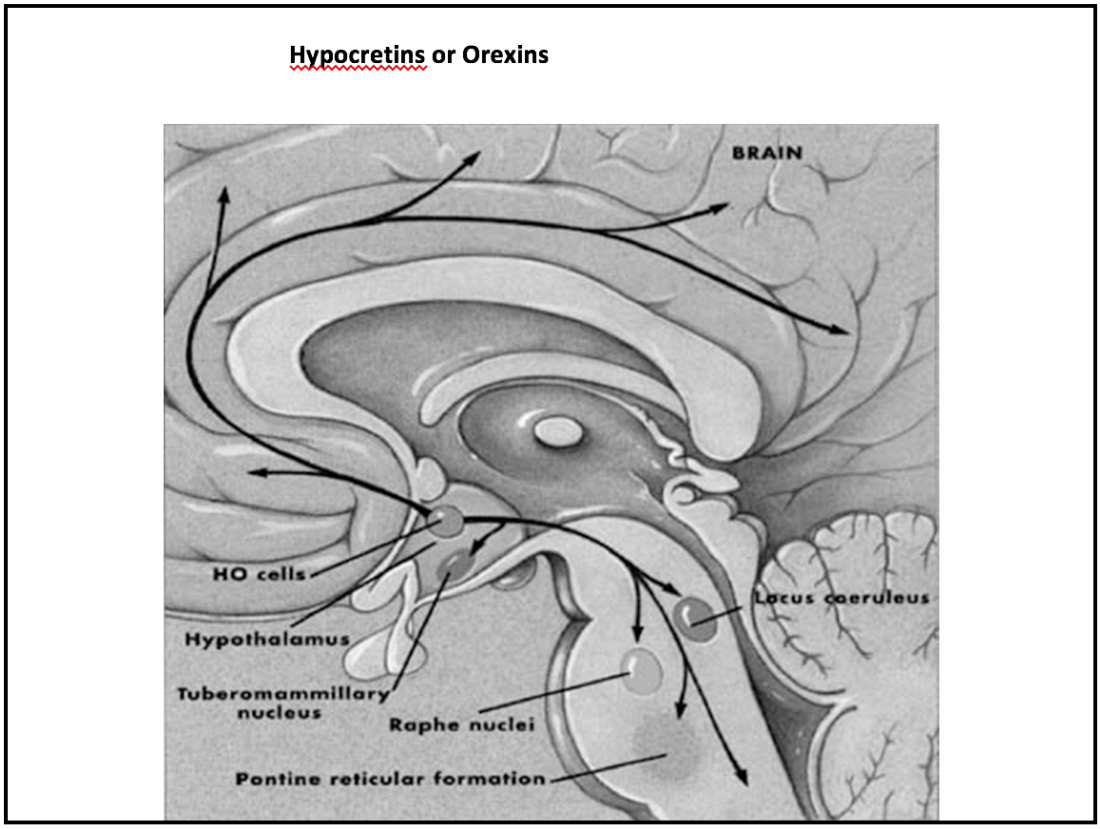
- **Provigil** (modafinil)
  - In US since 1998, in France for several years prior
  - Approvable letter (to treat ADHD) from FDA in 2005 but RELEASE DELAYED DUE TO RISKS OF DANGEROUS RASH AND OTHER RISKS (see below)
  - Promotes wakefulness, focus
  - No evidence of abuse; no evidence of withdrawal

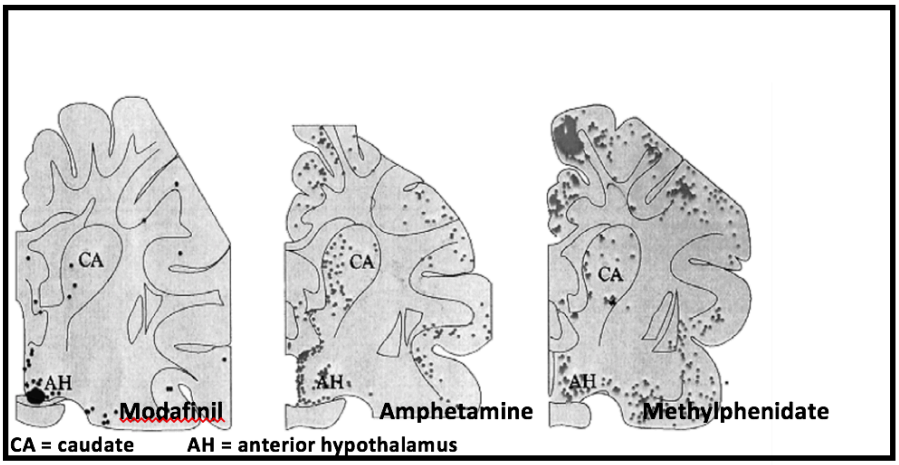


- Mechanism:
  - it increases histamine in the cortex (by increasing firing of histaminergic neurons in the hypothalamus)
  - it's actions appear to be dependent on alpha 1b adrenergic receptors as well as dopamine reuptake transporters.
  - also activates orexin neurons in the hypothalamus (though this may be result of wakefulness)



  -
  - also appears to increase serotonin, dopamine, and norepinephrine release in the cortex.
  - releases dopamine in the limbic cortex as well but to a more limited extent (and thus there is no apparent abuse liability)
  - it may block GABA action

Modafinil Demonstrates Highly Selective CNS Activity in Animal Studies



Modafinil is thought to work selectively in areas of the brain (e.g., anterior hypothalamus), believed to regulate normal wakefulness

Also binds weakly to Dopamine/Norepinephrine Transporter

- Evidence of efficacy
  - Children
    -

J Pediatr. 2008 Mar;152(3):394-9. doi: 10.1016/j.jpeds.2007.07.052. Epub 2007 Oct 24.

Modafinil improves symptoms of attention-deficit/hyperactivity disorder across subtypes in children and adolescents.

Biederman J[1], Pliszka SR.

OBJECTIVE:
This secondary analysis evaluated the efficacy of modafinil in children and adolescents by subtype of attention-deficit/hyperactivity disorder (ADHD) using pooled data from 3 double-blind, placebo-controlled studies.

STUDY DESIGN:
The patients were boys and girls age 6 to 17 years. ADHD subtype diagnoses (ie, inattentive, hyperactive-impulsive, combined) were based on criteria published in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Patients received modafinil (170 to 425 mg) or placebo once daily for 7 to 9 weeks. Efficacy assessment used the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School and Home Versions, Clinical Global Impression of Improvement scale (CGI-I), and Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).

RESULTS:
A total of 638 patients received modafinil (n = 423) or placebo (n = 215). The inattentive, hyperactive-impulsive, and combined subtypes included 187 (30%), 27 (4%), and 403 (65%) patients, respectively. Modafinil (vs placebo) significantly improved mean total scores for the ADHD-RS-IV School and Home Versions for the inattentive (change from baseline: School, modafinil, -15.7, placebo, -7.1; Home, modafinil, -13.8, placebo, -5.9) and combined subtypes (School, -16.5 vs -8.8; Home, -15.7 vs -7.6). Modafinil was associated with greater improvements on the CGI-I and improved CPRS-R:S subscale scores in inattentive and combined subtypes.

CONCLUSIONS:
Modafinil improved ADHD symptoms and behaviors in patients with the inattentive and combined subtypes as determined by teachers, investigators, and parents.

Published Modafinil Studies

- A randomized, double-blind and placebo-controlled trial of modafinil in children and adolescents with attention deficit and hyperactivity disorder. Kahbazi et al, 2009
- Modafinil improves symptoms of attention-deficit/hyperactivity disorder across subtypes in children and adolescents. Biederman et al, 2008
- Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. Amiri et al, 2008
- Efficacy and safety of modafinil film-coated tablets in children and adolescents with or without prior stimulant treatment for attention-deficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. Wigal et al, 2006
- A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. Biederman et al, 2006
- A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. Greenhill et al, 2006
- Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. Swanson et al, 2006
- Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. Biederman et al, 2005

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- Greenhill, Biederman, et al, 5/06, RCT, DB, placebo-controlled study of modafinil film-coated tablets in children with ADHD; 9-week study; 200 children ages 7-17; dose range 170-425 mg/day
    - 52% response rate versus 18% with placebo
    - Side effects
        - Insomnia 28% (vs 7% with placebo)
        - Headache 22% (vs 9% with placebo)
        - Decreased appetite 18% (vs 3% with placebo)
        - Abdominal pain 12% (vs 4% with placebo)) or nausea or diarrhea
        - Weight loss 5% (vs 1% with placebo)
        - Nervousness or anxiety
        - Not associated with drug high or withdrawal or tolerance.
        - No effect on sleep architecture.
        - Rash (in youth)
            - 12/933 (1.3%) with likely definitive dangerous rash (erythema multiforme or Stevens Johnson syndrome (SJS)) OR early prodromal rash OR suggestive dangerous rash, 1 of which was thought to be definitive SJS (though child was on an antibiotic medication as well).
            - No reports of SJS among 36,000 children prescribed the drug off-label between 2002-2005.
        - Rates similar (for medication vs. placebo) for infection, cough, pharyngitis, rhinitis, vomiting, emotional lability, nervousness, accidental injury, fever, tiredness, nausea
    - Side effects in the one-year open-label continuation phase of the studies in the Biederman review:
        - Insomnia 27% (vs. 4% with placebo)

        - Headache 20% (vs. 13% with placebo)
        - Decreased appetite 16% (vs. 3% with placebo)
        - Abdominal pain 10% (vs. 3-8% with placebo)
        - Nervousness 5% (vs. 4% with placebo)
        - No withdrawal or rebound effects
        - Mild decreases in weight from baseline for up to 3 months, then an increase in weight of 0.7 kg by month 12.
        - No significant changes in vital signs, weight, or height.
    - Biederman review of 3 randomized trials in youth aged 6-17 yo with ADHD (?overlaps with specific studies below)
        - 423 subjects receiving Provigil, 215 receiving placebo
        - Two nine-week studies, doses of 170-425 mg
        - One seven-week study, 340 mg/day
        - Safe and effective
    - 2005: multi-site, double-blind, placebo-controlled study in pediatric ADHD suggests efficacy.
    - Biederman, 2003 (partially funded by Cephalon): four week study of 248 children with ADHD demonstrated safety and efficacy
    - Swanson, 2003: four week study of 48 children demonstrated safety and efficacy
    - Rugino, 2003: positive safety and efficacy
    - Rugino, 2001: positive safety and efficacy comparable to Dexedrine
    - Fletcher, 2000: positive single site controlled study
    - 2000: failed multisite controlled trial
- Adults
    - ADHD
        - Turner, 2004: positive
        - Taylor, 2000: positive; equivalent in efficacy to Dexedrine
        - Overall potency in ADHD appears less than stimulants, Strattera, or atypical antipsychotics.
    - Depression
        - Promotes wakefulness in patients with depression

Modafinil in Depression

J Clin Psychiatry. 2013 Nov;74(11):1101-7. doi: 10.4088/JCP.13r08560.

Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials.

Goss AJ[1], Kaser M, Costafreda SG, Sahakian BJ, Fu CH.

OBJECTIVE:
Current pharmacologic treatments for a depressive episode in unipolar major depressive disorder (MDD) and bipolar depression are limited by low rates of remission. Residual symptoms include a persistent low mood and neurovegetative symptoms such as fatigue. The objective of this study was to examine the efficacy and tolerability of augmentation of first-line therapies with the novel stimulant-like agent modafinil in MDD and bipolar depression.

DATA SOURCES:
MEDLINE/PubMed, PsycINFO, 1980-April 2013 were searched using the following terms: (modafinil or armodafinil) and (depressi* or depressed or major depressive disorder or major depression or unipolar or bipolar or dysthymi*). Inclusion criteria were as follows: randomized controlled trial (RCT) design, sample comprising adult patients (18-65 years) with unipolar or bipolar depression, diagnosis according to DSM-IV, ICD-10, or other well-recognized criteria, modafinil or armodafinil given as augmentation therapy in at least 1 arm of the trial, and publication in English in a peer- reviewed journal.

STUDY SELECTION:
Double-blind, randomized, placebo-controlled clinical trials of adjunctive treatment with modafinil or armodafinil of standard treatment for depressive episodes in MDD and bipolar depression were selected.

DATA EXTRACTION:
Two independent appraisers assessed the eligibility of the trials. A random-effects meta-analysis with DerSimonian-Laird method was used. Moderator effects were evaluated by meta-regression.

RESULTS:
Data from 6 RCTs, with a total of 910 patients with MDD or bipolar depression, consisting of 4 MDD RCTs (n = 568) and 2 bipolar depression RCTs (n = 342) were analyzed. The meta-analysis revealed significant effects of modafinil on improvements in overall depression scores (point estimate = -0.35; 95% CI, -0.61 to -0.10) and remission rates (odds ratio = 1.61; 95% CI, 1.04 to 2.49). The treatment effects were evident in both MDD and bipolar depression, with no difference between disorders. Modafinil showed a significant positive effect on fatigue symptoms (95% CI, -0.42 to -0.05). The adverse events were no different from placebo.

CONCLUSIONS:
Modafinil is an effective augmentation strategy for acute depressive episodes, including for symptoms of fatigue, in both unipolar and bipolar disorders.

- Cognitive side effects of chemotherapy
- Schizophrenia
  - Pierre et al, 2007: improved global symptoms and functioning but not negative symptoms specifically
  - Improved cognitive function in schizophrenia (mixed results in Hunter et al, 2006)
- Binge Eating Disorder

Int Clin Psychopharmacol. 2015 Jul;30(4):209-15. doi: 10.1097/YIC.0000000000000079.
Armodafinil in binge eating disorder: a randomized, placebo-controlled trial. McElroy SL[1], Guerdjikova AI, Mori N, Blom TJ, Williams S, Casuto LS, Keck PE Jr. **Author information**

Abstract

This study evaluated the efficacy, tolerability, and safety of armodafinil in the treatment of binge eating disorder (BED). Sixty participants with BED were randomized to receive armodafinil (150-250 mg/day) (N = 30) or placebo (N = 30) in a 10-week, prospective, parallel-group, double-blind, flexible-dose, single-center trial. In the primary longitudinal analysis, armodafinil and placebo produced similar rates of improvement in binge eating day frequency (the primary outcome measure); however**, armodafinil was associated with a statistically significantly higher rate of decrease in binge eating episode frequency**. In the secondary baseline-to-endpoint analyses, armodafinil was associated with statistically significant reductions in obsessive-compulsive features of binge eating and BMI. The mean (SD) armodafinil daily dose at endpoint evaluation was 216.7 (43.9) mg. There were no serious adverse events, although one armodafinil recipient developed markedly increased blood pressure that resolved upon drug discontinuation. The small sample size may have limited the detection of important drug-placebo differences. As some of the observed effect sizes appeared clinically meaningful, larger studies of armodafinil in the treatment of BED are warranted.

- Side effects and risks in adults
  - headache
  - infrequent insomnia
  - infrequent anxiety
  - abdominal pain
  - loss of appetite
  - cough, fever
  - runny nose

Low incidence of "Switch" in Bipolar Depression

J Clin Psychiatry. 2014 Sep;75(9):1010-8. doi: 10.4088/JCP.13r08851.

A review of the use of stimulants and stimulant alternatives in treating bipolar depression and major depressive disorder.

Corp SA[1], Gitlin MJ, Altshuler LL.

OBJECTIVE:
Prescribers often consider the off-label use of stimulants or stimulant alternatives as adjunctive antidepressants. The authors reviewed the available literature on the efficacy of these agents for treatment of refractory unipolar and bipolar depression.

DATA SOURCES:
PubMed, MEDLINE, and relevant English-language literature from 1988-2013 were searched. Keywords were dopaminergic, stimulant, augmentation, treatment refractory depression, dextroamphetamine, methylphenidate, modafinil, atomoxetine, and cardiovascular safety.

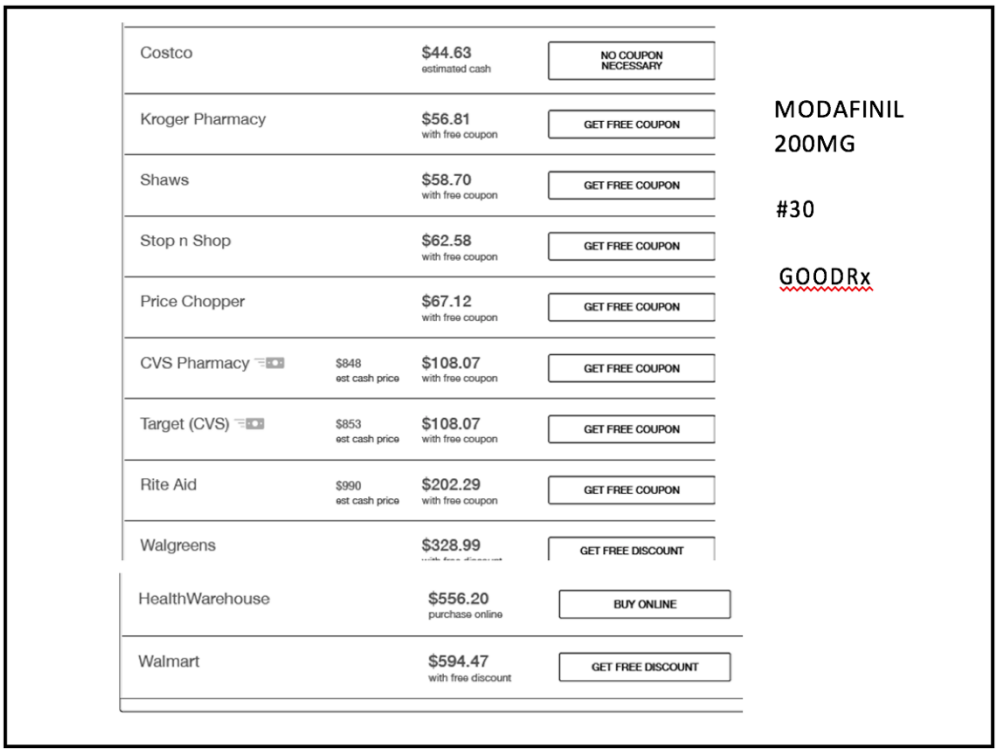
STUDY SELECTION:
All randomized controlled trials (RCTs) published during this time period were included. When RCTs were unavailable, open studies were summarized.

DATA EXTRACTION:
Data on the efficacy of stimulants and stimulant alternatives as treatment augmentation for unipolar and bipolar depression were extracted.

RESULTS:
Three open studies showed positive findings for dopaminergic stimulants, and, although 2 RCTs showed negative findings, a recent RCT revealed positive results for lisdexamfetamine as an adjunctive agent. To date, dopaminergic stimulants have not been tested in bipolar depression RCTs. Four completed RCTs suggested that modafinil/armodafinil were beneficial as treatment adjuncts for unipolar and bipolar depression, with very low rates of mood switch in bipolar depression. One study was stopped prematurely due to safety concerns of increased suicidality.

CONCLUSIONS:
Modafinil and armodafinil are recommended treatment adjuncts for refractory unipolar and bipolar depression. Until recently, RCT data on dopaminergic stimulants were too limited to warrant their use as first-line treatment adjuncts. However, the promising results of 1 recent lisdexamfetamine RCT, when considered in the context of the deleterious effect of subsyndromal depression, suggest consideration of dopaminergic medications in treatment-refractory unipolar or bipolar depression when modafinil is cost prohibitive or otherwise contraindicated.

- Pharmacology
  - induces 3A4 enzyme; can theoretically lower birth control
  - half-life 15 hours, time to max 2-4 hours
  - rebound sleepiness is minimal



- Nuvigil (armodafinil)
  - Single-isomer formulation of Provigil
  - Has longer half-life than Provigil
  - 150-250 mg/day
  - four multicenter double-blind studies demonstrating safety and efficacy (in sleep apnea), one of which:
    - 196 patients (aged 18-65 years) randomized to receive armodafinil 150 mg (n = 65), armodafinil 250 mg (n = 67), or placebo (n = 64) once daily for 12 weeks
    - statistically significant improvements in memory, attention, and fatigue
    - most common adverse events in patients receiving armodafinil were headache, nausea, and dizziness
  - Side effects
    - Headache 15% at 150 mg and 21% at 250 mg and in 7-8% of placebo
    - Nausea
    - Insomnia
    - Dizziness
    - Anxiety