Armodafinil (Nuvigil)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Armodafinil (Nuvigil®) is a central nervous stimulant that is indicated for wakefulness promotion in adults with narcolepsy, obstructive sleep apnea (OSA) and shift work disorder (SWD), which was approved by the FDA in June 2007.
- Armodafinil is the active R-enantiomer of the racemic product, modafinil.
- The VA National Formulary currently contains two other central nervous system stimulants, methylphenidate and dextroamphetamine.
- Non-formulary criteria for use (CFU) exist for the racemic product, modafinil.
- The mechanism of action for armodafinil is unclear, but is related to its activity as an inhibitor of dopamine reuptake at the dopamine transporter (DAT).
- The recommended dose for armodafinil is 150mg-250mg once daily for narcolepsy and OSA and 150mg once daily for SWD.
- One 12-week, multi-center, placebo controlled, parallel-group, double-blind study was used to establish efficacy of armodafinil for wakefulness promotion in adults with narcolepsy.
- Two 12-week, multi-center, placebo-controlled, parallel-group, double blind studies were used to establish efficacy of armodafinil for wakefulness promotion in adults with OSA.
- One 12-week, multi-center, placebo controlled, parallel-group, double-blind study was used to establish efficacy of armodafinil for wakefulness promotion in adults SWD.
- In a long-term safety trial of ≥12 months duration, the most commonly reported adverse events were headache (25%), nasopharryngitis (17%), insomnia (14%), and upper respiratory tract infections (10%). [25]
- In the same trial, serious adverse events were reported by 8% of the study population. These included chest pain (6 patients), myocardial infarction (4 patients), nephrolithiasis (4 patients), coronary artery disease (2 patients), hemorrhoidal hemorrhage (2 patients), cellulitis (2 patients), prostate cancer (2 patients) and hypertension (2 patients).
- Armodafinil is generally well-tolerated but increased monitoring of blood pressure may be appropriate in patients on armodafinil.
- Armodafinil is contraindicated in patients with established hypersensitivity to modafinil, armodafinil, or any inactive ingredients in the tablet.
- A precautionary statement is included for patients who develop a rash while on armodafinil as use of the drug has been associated development of serious rash requiring hospitalization, including Stevens-Johnson syndrome, in both adults and children.
- In two separate long-term, open-label extension trials, armodafinil maintained efficacy for wakefulness promotion for up to 12 months or longer.

Introduction

Armodafinil is a central nervous system stimulant that is indicated for wakefulness promotion in adults with narcolepsy, obstructive sleep apnea (OSA) and shift work disorder (SWD). This medication is the R-enantiomer of modafinil, another CNS stimulant. Armodafinil was approved by the FDA in June 2007.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating armodafinil for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1]

Mechanism of Action:
Armodafinil is the active R-isomer of modafinil. Its mechanism of action appears to be similar to that of other sympathomimetics including amphetamines, and possibly more specific to promoting wakefulness without other stimulatory actions as evidenced by animal model studies. Modafinil appears to have little to no activity at receptors for norepinephrine, serotonin, dopamine, histamine, gamma-aminobutyric acid, melatonin, or histamine-3. It is believed that the pharmacological activity of armodafinil is related to its activity as an inhibitor of dopamine reuptake at the dopamine transporter (DAT). This increase in extracellular dopamine may contribute to modafinil's abuse potential. Additionally, the stimulatory effects are attenuated by the coadministration of the alpha-adrenergic blocker prazosin which suggest additional theoretical mechanisms, but these theories have yet to be fully studied. The clinical significance of theoretical effect has yet to be elucidated.[1-2]

Pharmacokinetic properties:
The pharmacokinetic properties of armodafinil, modafinil, methylphenidate and dextroamphetamine are outlined below in Table 1. Armodafinil is prominently metabolized through amide hydrolysis and is also metabolized through CYP3A4 and CYP3A5. The two metabolites, R-modafinil acid and modafinil sulfone are inactive. It is unknown how armodafinil is eliminated through the body, but the racemic product, modafinil, is primarily eliminated through the kidneys (80%) with less than 10% unchanged. Armodafinil has a half-life of 15 hours. It is 60% protein bound in the bloodstream and the volume of distribution is estimated at 42L/kg. Taking armodafinil with food will delay the time to peak activity approximately 2-4 hours.[1-2]

Table 1. Pharmacokinetics of armodafinil and other CNS stimulants[1-4]

Parameter	Armodafinil	Modafinil	Methylphenidate	Dextroamphetamine
Metabolism	Amide hydrolysis (prominent) CYP3A4, CYP3A5	Deamination, S-oxidation, aromatic ring hydroxylation, glucuronidation, CYP3A4	Hydrolytic esterification	Oxidation via CYPD6
Metabolites	R-modafinil acid and modafinil sulfone (both inactive)	Modafinil acid and modafinil sulfone (inactive)	Ritalinic acid (inactive)	4-hydroxy amphetamine and norephedrine (active)
Elimination	unknown	Renal: 80% <10% unchanged Feces: 1%	Renal: 78-97% <1% unchanged Feces: 1-3%	Rena: 30-40% unchanged, 50% changed (can vary with urinary pH)
Half-life	15 hours	15 hours	d-isomer: 3-4 hours l-isomer: 1-3 hours	10-14 hours (varies based on age)
Protein Binding	60%, mainly albumin	~60%, mainly albumin	Low, 10-33%	
V_d	42 L/kg	0.9 L/kg	d-isomer:~ 2.65L/kg l-isomer: ~1.8 L/kg	3.5-4.6 L/kg, CNS concentration 80% of serum
Bioavailability	Not determined due to aqueous insolubility of armodafinil	Not determined due to aqueous insolubility of modafinil	d-isomer: 22% and l-isomer 5% (immediate release)	
Time to peak	Rapid; food delays approx 2-4 hours	Rapid; food slows absorption	1-2 hours; food slows absorption	3 hours (IR) 7 hours (XR)

FDA Approved Indication(s) [1]

Armodafinil is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea (OSA), narcolepsy and shift work disorder (SWD). There have been no systematic controlled studies beyond 12 weeks to determine the long-term efficacy of armodafinil; therefore, any physician who elects to prescribe armodafinil for greater than 12 weeks duration should periodically re-evaluate long-term usefulness for the individual patient as recommended by the packaging label provided by the manufacturer.

In OSA, armodafinil is indicated as an adjunct to standard treatment for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating armodafinil. If armodafinil is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary. In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.[5]

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Armodafinil could potentially be used to treat conditions for which modafinil is used off-label such as somnolence, attention deficit hyperactivity disorder, Parkinson's disease, bipolar depression augmentation and mytonic muscular dystrophy. Specific data regarding the efficacy of modafinil/armodafinil in these subsets of patients are included in the efficacy section.

Current VA National Formulary Alternatives

The following stimulants are alternatives to armodafinil on the VA National Formulary:

- Methylphenidate
  Dextroamphetamine
- Other alternatives available: Modafanil is non-formulary with criteria for use[6]

Dosage and Administration[1-3]

Obstructive Sleep Apnea (OSA) and Narcolepsy:
The recommended dose of armodafinil for treatment of both OSA and narcolepsy is 150 mg or 250 mg given as a single dose in the morning. In patients with OSA, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 150 mg/day dose

Shift Work Disorder (SWD):
The recommended dose of armodafinil for patients with SWD is 150 mg given daily approximately 1 hour prior to the start of their work shift.

Hepatic dose adjustments:

- In patients with severe hepatic impairment, armodafinil should be administered at a reduced dose

Renal dose adjustments:

- There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment

Elderly dosage adjustments:
In elderly patients, elimination of armodafinil and its metabolites may be reduced. Therefore, consideration should be given to the use of lower doses in this population

Other dosage adjustments:

- Concomitant medications that are substrates for CYP3A4/5, such as steroidal contraceptives, triazolam, and cyclosporine may be affected.
- Medications eliminated via CYP2C19 metabolism, such as diazepam, propranolol, and phenytoin may have prolonged elimination upon coadministration with armodafinil and may require dosage reduction and monitoring for toxicity
- Co-administration of armodafinil and monoamine oxidase inhibitors should be used with caution, as there are no specific data available evaluating this combination.

Efficacy

Efficacy Measures[7-8]

Clinical Global Impression of Change scale (CGI-C): 7- point rating scale to describe change in illness severity, accounting for total clinical experience. 1= most improved, 7= severely worsened
Clinical Global Impression of Severity scale (CGI-S): 7- point rating scale to describe severity of illness, accounting for total clinical experience. 1= normal, 7= severely ill
Epworth Sleepiness Scale (ESS): 24- point, 8 item scale used to measure the likelihood of falling asleep in particular situations. Items are rated 0 (would never fall asleep) to 3 (high chance of falling asleep).
Multiple Sleep Latency Test (MSLT): Objective measurement to determine level of sleepiness. Patients will lie in a quiet room and attempt a 20-minute nap at 2-hour intervals, 5 times. The time taken to reach different levels of sleep for 30 seconds is recorded.
Maintenance of Wakefulness Test (MWT): Objective measurement to determine level of sleepiness. Patients will lie in a dark room in a semi-reclined position and attempt to stay awake during 20 to 30 minute periods at 2-hour intervals, 6 times. The time taken to reach different levels of sleep for 30 seconds is recorded.

Summary of Evidence

Short term clinical trials have shown a statistically significant improvement in sleep latency in patients with OSA on CPAP, Narcolepsy, and SWD. Statistically significant differences in overall clinical improvement as defined by the CGI-C scale have also been demonstrated. Long term safety and efficacy has been described in 2 uncontrolled open-label extension studies for up to 12 months. These studies include subjects treated for OSA, SWD, and narcolepsy, but the methodology of these extension trials provides weak evidence.

Study limitations include short trial duration, small sample size, and lack of active comparators.

Table 2. Summary of prospective studies- evidence for armodafinil use[9-13]

					Outcome Measures			
Trial	**Design**	**Indication**	**n**	**Treatment**	**MSLT**	**MWT**	**CGI-C**	**p-value**
Czeisler 2009	12 week (R, DB, PC)	SWD	254	ARM 150 MG Placebo	↑ 3.1 min ↑0.4 min	X	79% 59%	<0.001 MSLT 0.001 CGI-C
Harsh 2006	12 week (R,DB PC)	Narcolepsy	196	ARM 150 MG ARM 250 MG Placebo	150 + 250: ↑ 1.9 min ↓ 1.9 min	X	150 + 250: 71% 33%	<0.01 MSLT <0.001 CGI-C
Hirshkowitz 2007	12 week (R, DB, PC)	OSA	259	ARM 150 MG Placebo	X	↑ 2.3 min ↓ 1.3 min	71% 53%	0.0003 MWT 0.0068 CGI-C
Krystal 2010	12 week (R, DB, PC)	OSA, comorbid depression	249	ARM to 200 MG Placebo	↑ 2.6 min ↑ 1.1 min	X	69% 53%	NS MSLT 0.03 CGI-C
Roth 2006	12 week (R, DB, PC)	OSA	395	ARM 150 MG ARM 250 MG Placebo	X	Active arms improved (data not provided)	Active arms improved (data not provided)	ARM 150 p=0.01 MWT Combined <0.001 MWT <0.001 CGI-C

R= randomized, DB= Double blind, PC= placebo controlled. All subjects enrolled had CGI-S scores ≥4 at time of initiation. Subjects with OSA were required to have adequate continuous positive airway pressure (CPAP) use during trials.

Efficacy of Off-label Uses:

- Attention deficit hyperactivity disorder

  - Clinical trials suggest efficacy of modafinil in children and adolescents with ADHD. The drug did not receive FDA approval for this indication likely due to incidence of severe dermatological adverse reactions
  - Large dose finding RCTs up to 9 weeks in duration examining modafinil in adults with ADHD have found no statistically significant benefit when compared to placebo[14]
- Parkinson's disease
  - Small RCTs of modafinil have yielded inconsistent results. [14-15]
    - 12-37 subjects, 1 parallel group, 2 crossover studies 4-7 weeks in duration
    - 2 studies demonstrated improvement in Epworth Sleepiness Scale, 1 study demonstrated no significant improvement
- Augmentation of bipolar depression[14,16]
  - A 257 subject, 8 week RCT of armodafinil versus placebo in patients experiencing bipolar I depression while on lithium, valproic acid, or olanzapine
    - Some improvement of the Inventory of Depressive Symptomatology, Clinician-rated score, but no statistically significant difference in the Montgomery-Asberg Depression Rating Scale and other symptom measurements. More studies are required to further elucidate antidepressant effects of armodafinil.
- Myotonic muscular dystrophy [17]
  - Small RCTs of modafinil suggest mixed levels of improvement in daytime sleepiness in this population
    - 3 studies with a total of 87 patients with up to 4 weeks of active treatment found reductions in ESS and/or MWT
    - 1 study examined 28 patients up to 4 weeks found no significant improvement in ESS or MWT
- Fibromyalgia fatigue[18]
  - Limited data supporting armodafinil use
- HIV- Related fatigue[19-20]
  - Small studies with supportive results utilizing both modafinil and armodafinil
- Cognition and fatigue improvement in schizophrenia[21-22]
    - Small studies of armodafinil with negative results
- Traumatic Brain Injury (TBI) related excessive daytime sleepiness (EDS)[23-24]
  - There have been a few small studies examining the effects of modafinil on EDS associated with TBI
    - Results suggest an improvement in sleepiness but not fatigue

For further details on the efficacy results of the clinical trials, refer to (page 13).

Adverse Events (Safety Data)[1-2, 25-28]

Deaths and Other Serious Adverse Events

In a long-term safety trial of ≥12 months duration, serious adverse events were reported by 8% of the study population. These included chest pain (6 patients), myocardial infarction (4 patients), nephrolithiasis (4 patients), coronary artery disease (2 patients), hemorrhoidal hemorrhage (2 patients), cellulitis (2 patients), prostate cancer (2 patients) and hypertension (2 patients).

In postmarketing surveillance data of modafinil, no overdoses have been reported. However, fatalities have occurred in patients taking multiple drugs including modafinil.

Common Adverse Events

The most common reported adverse events reported for armodafinil were headache, nausea, dizziness and insomnia. The common adverse events are outlined in table 3. In a long-term safety trial over ≥12 months, the most commonly reported adverse events were headache (25%), nasopharryngitis (17%), insomnia (14%), and upper respiratory tract infections (10%).

Table 3. Common Adverse Events, n

ORGAN/ SYSTEM	ARM 250 MG (N= 198)	ARM 150 MG (N= 447)	COMBINED* (N= 645)	PLACEBO (N= 445)
Gastrointestinal				
-Nausea	9	6	7	3
-Dry mouth	7	2	4	<1
CNS				
-Headache	23	14	17	9
Psychiatric				
-Insomnia	6	4	5	1
-Depression	3	1	2	<1
Skin				
-Rash	4	1	2	<1

*Data reflects use of both armodafinil 150 mg and 250 mg as a composite

Other Adverse Events

The dose-dependent adverse events occurring in the controlled trials at an incidence of >1% are summarized in table 4.

Table 4. Dose-dependent adverse effects occurring >1% incidence, %

ORGAN/ SYSTEM	COMBINED (N= 645)	PLACEBO (N= 445)
Cardiac		
Palpitations	2	1
Gastrointestinal		
Nausea	7	3
Diarrhea	4	2
Dry mouth	4	<1
Dyspepsia	2	0
Abdominal pain	2	1
Constipation	1	0
Vomiting	1	0
Loose stool	1	0
CNS-		
Headache	17	9
Dizziness	5	2
Attention disturbance	1	0
Tremor	1	0
Migraine	1	0
Parasthesia	1	0
Psychiatric		
Insomnia	5	1
Anxiety	4	1
Depression	2	0
Agitation	1	0
Nervousness	1	0
Depressed mood	1	0
Repisratory		
Dyspnea	1	0
Renal		
Polyuria	1	0
Skin/ Subcutaneous tissue		
Rash	2	0
Contact Dermatitis	1	0
Hyperhydrosis	1	0
Immune		
Seasonal allergy	1	0
Metabolic/Nutritional		
Anorexia	1	0
Decreased appetite	1	0
Laboratory/Physical findings		
Gamma-glutamyltransferase increased	1	0
Increased heart rate	1	0
General		
Fatigue	2	1
Thirst	1	0
Influenza-like symptoms	1	0
Pain	1	0
Pyrexia	1	0

Tolerability
Discontinuation due to an adverse event occurred at relatively low rates in both the armodafinil and placebo arms in the clinical trials. In patients who received armodafinil, 7% discontinued the treatment due to an adverse event versus 4% of the patients who received placebo. Armodafinil is found to be generally well tolerated in the clinical trial populations. Most adverse events were mild to moderate.

For further details on the safety results of the clinical trials, refer to (page 13).

Contraindications

- Patients with established hypersensitivity to modafinil, armodafinil, or its inactive ingredients.

Warnings and Precautions

Serious Rash:

- Serious rash requiring hospitalization and discontinuation of therapy, including Stevens-Johnson syndrome, has been reported in both adults and children in association with the use of armodafinil.

Angioedema and Anaphylaxis:

- In the adult clinical trials of armodafinil (n=1595), one case of angioedema and one case of hypersensitivity were reported.

Multi-organ Hypersensitivity Reactions:

- Multi-organ hypersensitivity has occurred in close temporal association with the initiation of modafinil, including one fatality. No incidences have been reported with armodafinil, but similar risk cannot be ruled out.

Persistent Sleepiness:

- Patients with excessive sleepiness should be reassessed for level of sleepiness after initiation of armodafinil. Patients level of wakefulness may not return to normal after initiation of armodafinil.

Psychiatric Symptoms:

- During postmarketing surveillance of modafinil, adverse events have been reported including mania, delusions, hallucinations, suicidal ideation and aggression. The incidence and type of psychiatric event is likely to be similar with armodafinil.

Cardiovascular Risk:

- Based on studies of modafinil, armodafinil should not be uses in patients with left ventricular hypertrophy or in patients with history of mitral valve prolapsed syndrome when previously receiving CNS stimulants.

Special Populations

Pregnancy:

- Armodafinil is considered a pregnancy category C
- In studies of pregnant rats exposed to armodafinil and modafinil during organogenesis, there were increased incidences of fetal visceral and skeletal variations and decreased body weight at the intermediate and highest doses respectively.
- In studies of pregnant rabbits exposed to modafinil during organogenesis, incidences of fetal structural alterations and embryofetal death were increased at the highest dose. The no-effect

dose for developmental toxicity in rabbits corresponds to the AUC in humans at the recommended highest dose.
- No adequate studies exist in pregnant women. There are three case reports (two cases of intrauterine growth retardation and one spontaneous abortion) were associated with use of modafinil and armodafinil.

Breast Feeding:
- It is unknown if armodafinil or its metabolites are excreted in breast milk.

Pediatrics:
- The safe and effective use of armodafinil in patients under the age of 17 has not been established.

Geriatrics:
- Elimination of armodafinil and its metabolites may be reduced in elderly patients.

Sentinel Events
No data available.

Look-alike / Sound-alike (LA / SA) Error Risk Potential
As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from two data sources (Lexi-Comp and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 5. Look-alike/Sound-alike assessment

	Lexi-Comp	ISMP	Clinical Judgment
Armodafinil	None	None	Modafinil
Nuvigil®	None	None	Nucynta® Provigil®

Drug Interactions

Drug-Drug Interactions
- Armodafinil is a moderate inducer of CYP3A4, CYP3A5
  - Decreased effectiveness of oral contraceptives, midazolam, triazolam, and cyclosporine, and nimodipine may result
- Armodafinil is a moderate inhibitor of CYP2D19
  - Increased exposure and risk of toxicity with phenytoin, diazepam, clomipramine, propranolol, and omeprazole
  - Increased frequency of international normalized ratio (INR) recommended in patients receiving warfarin therapy
- Co-administration of armodafinil and monoamine oxidase inhibitors should be used with caution, as there are no specific data available evaluating this combination.

Drug-Lab Interactions
- In patients who were administered armodafinil, mean plasma levels of gamma gllutamyltrasnferase (GGT) and alkaline phospatase (AP) were found to be higher than in patients who received placebo but mostly remained within normal limits.

- A single case of pancytopenia occurred during the clinical trials but resolved with drug discontinuation.

Drug-Disease Interactions

- Vital sign changes
  - The average increase in pulse rate between patients who received armodafinil varied from 0.9-3.5 beats per minute
  - Small increases in average values for mean systolic and diastolic blood pressure readings were seen in patients given armodafinil in clinical studies.
- A slightly greater proportion of patients given armodafinil in clinical studies required either new or increased doses of antihypertensive medications.

Drug Abuse and Dependence

Controlled Substance Class

Armodafinil is a Schedule IV controlled substance.

Abuse Potential and Dependence

Based on studies with modafinil, the abuse potential of armodafinil is expected to be similar. Modafinil has been reported to produce euphoria, alterations in mood, perception, thinking and feelings. These findings are similar to other CNS stimulants, including VA national formulary agent methylphenidate. In vitro, modafinil has been shown to bind with dopamine reuptake sites causing an increase in extracellular dopamine.

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

There are currently no published pharmacoeconomic data in regards to armodafinil.

Conclusions

- Armodafinil appears similar to modafinil in terms of safety and efficacy for management of FDA-labeled indications, with small pharmacokinetic differences
- In the treatment of narcolepsy, methylphenidate and dexamphetamine are less expensive with no well-studied differences in efficacy
- In the treatment of excessive sleepiness associated with shift work disorder and obstructive sleep apnea, modest benefits may be seen in patients with persistent symptoms despite appropriate non-pharmacological interventions
- Armodafinil is more costly than formulary stimulant agents, and is currently less costly than modafinil. Armodafinil may be considered for preference of non-formulary agent due to similarities between itself and modafinil.
- There are extensive, mixed data in regards to off-label potential uses for armodafinil.

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Appendix: Clinical Trials

A literature search was performed on PubMed and www.clinicaltrials.gov 2001-November 2012 using the search terms "armodafinil" and "nuvigil", limited to human clinical trials. Reference lists of review articles and

manufacturer's labeling information were also searched for relevant clinical trials. All randomized contolled trials published in peer-reviewed journals were included.

Study	Eligibility Criteria	Intervention	Patient Population	Efficacy Results	Safety Results	Conclusions/ Critique
Czeisler et al. *Mayo Clin Proc* 2009; 84(11): 958-72 12 week R, DB, PC, MC	**Inclusion:** - 18- 65 years old -Excessive sleepiness during night shifts ≥ 3 mo -MSLT ≤ 6 min -Insomnia* -SWD clinically judged moderate to severe **Exclusion:** -Significant substance abuse or psychiatric disorder -Sensitivity to agent or other stimulants	-A 150 mg -P Received 30-60 minutes prior to shift	**Age**: (A) 40, (P) 39 **Male %:** (A) 52, (P) 54 **White race %:** (A) 70 (P) 60 **CGI-S severe %:** (A) 7 (P) 9 **Shift-work "permanent" %:** (A) 87 (P) 89	N_R = 245 A: N = 1 2 2 P: N = 1 2 3 **MSLT**: (A) ↑ 3.1 min (P) ↑ 0.4 min p < 0.001 **CGI-C improvement:** (A) 78 % (P) 56% p=0.001 Patient reported levels of unintended sleep, memory, attention, and sleepiness during shift improved in (A).	**Adverse events:** Headache (A) 12% (P) 10% Nausea (A) 7% (P) 3% Nasopharyngitis (A) 6% (P) 3% Anxiety (A) 5% (P) 2% -1 subject in armodafinil group withdrew due to suicidal ideation	Armodafinil,significantly improved measures of sleep propensity, subjective sleepiness, memory, and attention during scheduled night work hours in patients with excessive sleepiness associated with SWD without disturbing daytime sleep. *Population limited, mostly individuals permanently on overnight shift*
Harsh et al. *Cur Med Res Opin.* 2006; 22(4): 761-74 12 week R, DB, PC, MC	**Inclusion:** - 18-65 years old -ICSD diagnosed narcolepsy -MSLT ≤ 6 min -CGI-S score ≥ 4 -No other medical or psychiatric conditions which may be contributing to excessive sleepiness **Exclusion:** -Consumes ≥ 600 mg of caffeine/ day - Significant substance abuse -Sensitivity to agent or other stimulants	-A 250 mg -A 150 mg -P Dosing every morning	**Age**: 38.1 **Male :** 85/196	N_R = 196 A250: N = 65 A150: N = **MWT**: A250: ↑ 2.6 min A150: ↑1.3 min Combined: ↑ 1.9 min P: ↓ 1.9 min p= 0.0024 **CGI-C improvement:** A250: 73% A150: 69% Combined: 71% P: 33% p=0.0001 Both doses had improvements in memory, attention, and fatigue based off patient self-reported scales p=0.05	**Adverse events:** Nausea, A250: 7% A150: 14% P: 0% Nasopharyngitis A250: 4% A150: 3% P: 8% Decreased appetite A250: 6% A150: 3% P: 0% Headache A250: 28% A150: 16% P: 11% Dizziness A250: 3% A150: 8% P: 0% -1 subject developed angioneurotic edema	Armodafinil significantly improved ability to sustain wakefulness throughout the day, overall clinical condition, memory, attention, and fatigue when compared with placebo. *Statistical analysis examined combined 150/250 mg data compared with placebo*
Hirshkowitz et al. *Respir Med.* 2007;101(3):616-627. 12 week R, DB, PC,	**Inclusion:** -Age 18-65 years -Diagnosed with OSA/HS -Complaints of residual excessive sleepiness with	-A 150 mg -P Armodafinil was titrated from	**Age: (**A) 50.6 (P) 50.7 **Male %**:(A) 72 (P)75 **White Race%:** (A) 85 (P) 83	N_R = 259 A: N = 1 2 9 P: N = 1 3 0	**Adverse events more frequent vs placebo:** Nausea, A: 5% P: 3% Decreased appetite A: 14% P: 0% Headache A: 15% P: 7%	Armodafinil was well tolerated and improved overall condition, fatigue, and alertness as adjunctive treatment in OSA with nCPAP adherence.

MC	regular nCPAP use ≥ 4 hr per night, ≥70% of nights over 2 weeks -CGI-S ≥ 4 -ESS ≥ 10/24 **Exclusion:** -Psychiatric or medical condition that may contribute -Consumes >600mg caffeine/day -History of drug/ETOH use -Medically required to use drugs disallowed by protocol	50-150 mg over 4 day period, taken daily before 8AM and 30 minutes before breakfast	**CGI-S severe %:** (A) 10 (P) 14 **ESS:** (A) 16 (P) 15.6	**MWT**: (A) ↑ 2.3 min (P) ↓ 1.3 min p = 0.0003 over 1st 4 tests early in day, NS later in day (1500, 1700, 1900). **CGI-C improvement:** (A) 71 % (P) 53% p=0.0069 Patient episodic secondary memory from cognitive drug research battery improved significantly vs placebo. Improvement in ESS also noted statistically significant.	Dizziness A: 5% P: 2% Diarrhea: A: 5% P: 2% Anxiety: A: 5% P: 0% 5/129 subjects randomized to modafinil stopped due to adverse event, including 2 who developed rash. 5/130 patients in placebo group stopped due to adverse event, 1 who developed rash.	*May not be as applicable to individuals outside sample group (white males with established nCPAP adherence)*
Roth T et al. *Clin Ther* 2006; 28(5):689-706. 12 week R, DB, PC, MC	**Inclusion:** -Men and women aged 18 to 65 years -Diagnosis of moderate OSA/HSwith residual sleepiness -despite regular, effective and stable nCPAP regimen **Exclusion:** -any medical or psychiatric condition that could contribute to ES -a probable diagnosis of a sleep disorder other than OSA/HS -any disorder that might interfere with drug ADME -a history of alcohol or drug abuse -consumption of >600 mg/d of caffeine -clinically significant drug sensitivity to central nervous	A 150mg A 250 mg P titrated form 50 to 150 mg over 4 days; and from 50 to 250mg over 8 days Drug taken daily before 8AM and 30minutes before breakfast except on clinic days when given at 7AM	**Age: (**A) 49.2 (P) 50.1 **Male %**:(A) 71 (P)69.2 **White Race%:** (A) 84 (P) 86.9 **CGI-S severe %:** (A) 13 (P) 16.9 **ESS:** (A) 15.4(P) 15.9	N_R = 395 A250 N = 131 A150 N=133 **MWT**: (A) ↑ 1.9 min (P) ↓ 1.7 min p< 0.001 over morning and afternoon tests **CGI-C improvement:** (A) 72% (P) 37% P<0.001 **Change from baseline ESS scores:** (A) -5.5 (P) -3.3; p< 0.001 **Changes from baseline BFI scores:** (A)-1.2(P)-0.6; p<0.01	**Adverse events more frequent vs placebo:** Headache, A:17.6% P:8.5% Insomnia, A:6.5% P:1.5% Dry Mouth, A:4.2% P:0% P<0.05 **Severe adverse events**:-ulcerative colitis, migraine, worsening of Axis II and mood disorder, and duodenal ulcer) were reported in 4 (1.5 %)patients receiving armodafinil. No significant effects on nighttime sleep,as assessed using polysomnography, were found with armodafinil.	Armodafinil was well tolerated, with no adverse effect on nighttime sleep or nCPAP use, benefits shown at first visit and maintained for duration of trial

	system stimulants or modafinil. -pregnant or breastfeeding					
Krystal AD et al. *J Clin Psychiatry* 2010; 71(1): 32-40 12 week R, DB, PC, MC	**Inclusion:** Age 18-65 years -Diagnosed with OSA/HS -Complaints of residual excessive sleepiness with effective CPAP use ≥4 weeks -CGI-S ≥ 4 -ESS ≥ 10/24 -DSM-IV diagnosed depression or dysthymic disorder -HDRS-17 score <17 **Exclusion:** -Confirmed or suspected sleep disorder other than OSA -Treatment resistant depression -Other Axis I or II diagnoses+ -Score ≥2 on suicidality scale in HDRS-17 -History of substance abuse/ dependence	-Flexible dose armodafinil titrated from 50 mg to goal 200 mg, max 250 mg Titrated by 50 mg increments on days 2,5 and 8. Could be adjusted up to 3 weeks after initiation; once dose decreased it may not be increased -Placebo	**Age: (**A) 49.5 (P) 49.5 **Male %**:(A) 46 (P) 47 **White Race%:** (A) 90 (P) 90 **HDRS-17:** (A) 6.7 (P) 6.3 **CGI-S severe %:** (A) 11 (P) 10 **ESS:** (A) ↓ 6.3 (P) ↓ 4.8 **MWT (min):** (A) 20 (P) 21.3	N_R= 249 A n=125 P n=124 **MWT**: (A) ↑2.6 min (P) ↑ 1.1 min (not sig) **CGI-C improvement:** (A) 69% (P) 53% p=0.012 **Change from baseline ESS scores:** (A) -5.5 (P) -3.3; p< 0.001	**Adverse events more frequent vs placebo:** Headache A: 11% P: 7% Dry mouth A: 10% P: 0% Insomnia: A: 9% P: 2% Nausea, A: 5% P: 3% Anxiety: A: 6% P: 1% No patients reported suicidal ideation, hypomania, or mania. **Discontinuation due to tolerability:** A: 12 P: 7 In A group, d/c due to dry mouth, headache, dyspnea, and disturbance of attention	Comorbid depression with OSA treated with armodafinil is generally well tolerated but does not appear to directly affect depression. MWT, however, failed to reach statistical significance in this study.
Calabrese JR, et al. *J Clin Psychiatry* 2010;71(10): 1363-70 8 week R, DB, PC, MC	**Inclusion:** -Male / female 18-65 years -Experiencing depressive episode associate with Bipolar I disorder, 4 weeks- 12 months in duration -QIDS-SR_{16} ≥13 -CGI-BP for depression ≥4 -YMRS <10 -Unresponsive to lithium, valproic acid, or olanzapine	-Armodafinil 150 mg every morning -Placebo	**Age: (**A) 42.6 (P) 44.9 **Male %**:(A) 50 (P) 41 **White Race%:** (A) 68 (P) 71 **IDS-C_{30}:** (A) 37.4 (P) 36.3 **MADRS:** (A) 26.6 (P) 27.3 **QIDS-SR_{16}:** (A) 16.3 (P) 15.9	N_R= 257 A n=128 P n=129 **IDS-C_{30}**: (A) -15.8 (P) -12.8 p=0.0439 at 4 weeks, did not reach significance at each visit **MADRS, CGI-BP, QIDS-SR, HARS, YMRS** all non significant (A) -5.5 (P) -3.3;	**Adverse events more frequent vs placebo:** Headache A: 11% P: 10% Diarrhea A: 10% P: 6% Insomnia: A: 10% P: 8% Nausea, A: 7% P: 5% Dry mouth: A: 6% P: 4% Restlessness: A: 6% P: <1% Somnolence: A: 5% P: 2% **Discontinuation due to**	Armodafinil 150 mg / day was well tolerated and improved some, but not all, measured level of depression in patients with Bipolar I disorder experiencing a depressive episode currently on lithium, valproic acid, or olanzapine. *Most scales were not statistically significant. Larger-scale studies to further examine this potential effect are necessary.*

	for 8 weeks **Exclusion:** -Started psychotherapy within 2 months -Severe uncontrolled medical condition -Active/ interfering Axis I or II disorders+ -Active psychotic symptoms -Substance abuse -Stimulant induced mania -Insomnia -Previous use/ hypersensitivity -			p< 0.001	**tolerability:** Not discussed in study	
Bobo WV, et al. *Schizophrenia Res.* 2011; 130(1-3): 106-113. 6 week R, DB, PC	**Inclusion** -male/female Ages 18-64- -DSM IV criteria for schizophrenia/ schizoaffective -on stable doses of antipsychotic ≥2 mos with no other psychotropic meds besides SSRIs **Exclusion** -concomitant mood stabilizers, non-SSRI antidepressants, anticholinergic medications, benzodiazepines - pregnant/nursing -exposure to armodafinil within 4 wks of study -history of sensitivity to modafinil/ armodafinil -acute exacerbation of psychiatric	A 150mg P -once daily in the morning -fixed dose throughout study	M Gender%: (A) 51.7 (P) 69.0 White Race%: (A) 44.8 (P) 37.9 Diagnosis: Schizophrenia% (A) 58.6 (P)55.1 Schizoaffective% (A) 41.4 (P) 44.9 Age (mean):(A) 44 (P) 38.8 Age of onset (mean years): (A) 21.2 (P) 38.8 Duration of illness: (A) 22.9 (P) 17.5	N_R=58 Significant drug x time interaction for attention/vigilance for armodafinil [CPT-Pairs d', F(1,40)=6.2, p=0.017] No significant differenceafter corrections for multiple comparisons. No difference in other cognitive domains or psychopathology measures. Armodafinil associated with significant difference in SANS anhedonia-asociality [F(1,41)=4.1, p=0.05]	**Adverse events** No significant differences between groups for any adverse events **Discontinuation due to adverse event** (A) N=3, (P) N=1	No significant difference in neurocognitive measures between armodafinil and placebo groups. Armodafinil improved anhedonia-asociality but not other negative symptom domains. *Armodafinil dose may have been too low. May not be applicable to most schizophrenic patients on multiple psychotropic drugs.*

	illness req. hospitalization within 8 wks of study -presence of general comorbidity that precluded entry into trial					
Kane JM, et al. *Schizophrenia Res.* 2012; 135:116-122. 24 week R, DB, PC, MC,	**Inclusion** -Male/female Age 18-65 -DSM IV criteria for schizophrenia -receiving treatment with olanzapine, risperidone, paliperidone for ≥6 weeks, stable dose for≥4 wks -clinically stable for ≥8wks prior to baseline visit -PANSS negative symptom score≥15 (amended inclusión) **Exclusion** -PANSS positive symptom score≥4 -comorbid Axis I disorder -moderate to severe depression on CDSS -current suicidal ideation or previous suicide attempt -moderate or worse CDSS suicide ítems score (≥2) -homicidal ideation or aggression -stimulant-induced psychotic episode -exacerbation of illness -substance abuse or dependence within 6 mos -seizure disorder -clinically	A 150mg A 200mg A 250mg Placebo Once daily in the morning -all pts began at 50mg (or placebo equivalent) -doses titrated 50mg Q2days until target dose reached	**Age (mean years):** (A) 43.8 (P) 42.4 **Male gender %:** (A) 75 (P) 64 **White race %:** (A) 47 (P) 52 **BMI (mean):** (A) 31.3 (P) 31.8 **Times since onset (mean years):** (A) 18 (P) 16.7 **#psych hospitalizations (mean):** (A) 5.0 (P) 4.3 **Prior antipsychotic drug (risperidone %):** (A):53 (P) 39	N_R=285 A150 n=71 A200 n=70 A250 n=72 Change in PANSS negative symptom score (A150) -1.9 (3.8) (A200) -2.3(3.6), (A250)-2.0 (3.3) (P) -2.2 (4.1) (p≥0.7) Secondary measures generally not different.	**Adverse events more frequent vs placebo:** Headache (15%), initial insomnia (9%), nausea (7%), dry mouth (5%), cough (5%) Severe AEs (A) n=12 (6%) (P) n=5 (7%) **Reported severe AEs: *armodafinil(#)*:** Schizophrenia exacerbation (4), suicidal ideation (1), alcohol abuse (1), bacterial arthritis (1), conversion disorder (1), delusion (1), drug abuse (1), knee operation (1), uncontrolled DM (1), paranoia (1), suicide attempt (1) **Placebo (#):** adjustment disorder (1), heat exhaustion (1), psychotic disorder (1), suicidal ideation (1)	No clinically or statistically significant difference in PANSS negative symptom subscale (primary endpoint). No difference in secondary measures (PANSS total score, CGI-S, PSP, CNSVitalSIgns cognitive battery). Armodafinil well-tolerated. *Inclusion criteria modified mid study (PANSS baseline score) to maximize difference.*

	significant brain surgery/trauma -ECT -tardive dyskinesia -any significant movement disorder					
Rabkin JG et al. *Pyschosomatics* 2011;52: 328-336 4 week R, DB, PC + 26 weeks open label	**Inclusion:** -HIV + - 21-70 years of age -Clinically significant fatigued interfering with ≥ 2daily activities on a RFS -≥41 on a FSS **Exclusion:** - Change in antivirals/ antidepressants -Unstable/ untreated conditions including depresison or conditions that may contribute to fatigue -Current/recent substance use disorder	-50 mg armodafinil -Titrate by 50 mg weekly until effect, max 250 mg. -Placebo	**Age: (**A) 46 (P) 46 **Male %**:(A) 86 (P) 88 **White Race%:** (A) 47 (P) 50 **DSM-IV diagnosed depression %:** (A) 39 (P) 40 **ESS:** (A) 14.6 (P) 14.0	N_R= 70 A n=36 P n=34 75 % receiving armodafinil were responders (CGI-C of 1 or 2) vs 26% placebo (p <0.0001) (NNT=2) at week 4 -Significant improvements in ESS, RFS, and CFS -Adjusted HRSD and BDI not significantly improved	**Adverse events more frequent vs placebo at week 4:** Headache A: 19% P: 6% (p= 0.09) **Discontinuation due to tolerability:** A: 1 P: 2 1 patient discontinued at end of 4 weeks due to feeling "hyper"	Armodafinil appears safe and effective for patients with clinically significant fatigue associated with HIV. No significant changes were noted in regards to depressive symptoms or changes in CD4/ Viral load. *Single-center study limits, small sample size, and exclusion criteria*

ICSD= International Classification of Sleep Disorders

N_R, Number randomized. R= randomized, DB= Double blind, PC= placebo controlled, MC= Multicenter. A= armodafinil P= Placebo RFS= Role function scale FSS: Fatigue severity scale YMRS= Young Mania Rating Scale IDS-C$_{30}$ = 30-Item Inventory of Depressive Symptomatology, Clinician Rated MADRS= Montgomery- Asberg Depression Rating Scale QIDS-SR: 16-item Quick Inventory of Depressive Symptomatology. Insomnia: sleep efficiency ≤87.5% during daytime sleep

+ Axis I diagnoses may include schizophrenia and bipolar disorder. Axis II diagnoses may include borderline personality disorder and antisocial personality disorder.