

High-Dose Armodafinil in Treatment-Resistant Bipolar Depression: A Case Report

Wan Kwok, BA¹, Victoria Eby, MD¹, & Henry Nasrallah, MD¹

¹Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati College of Medicine

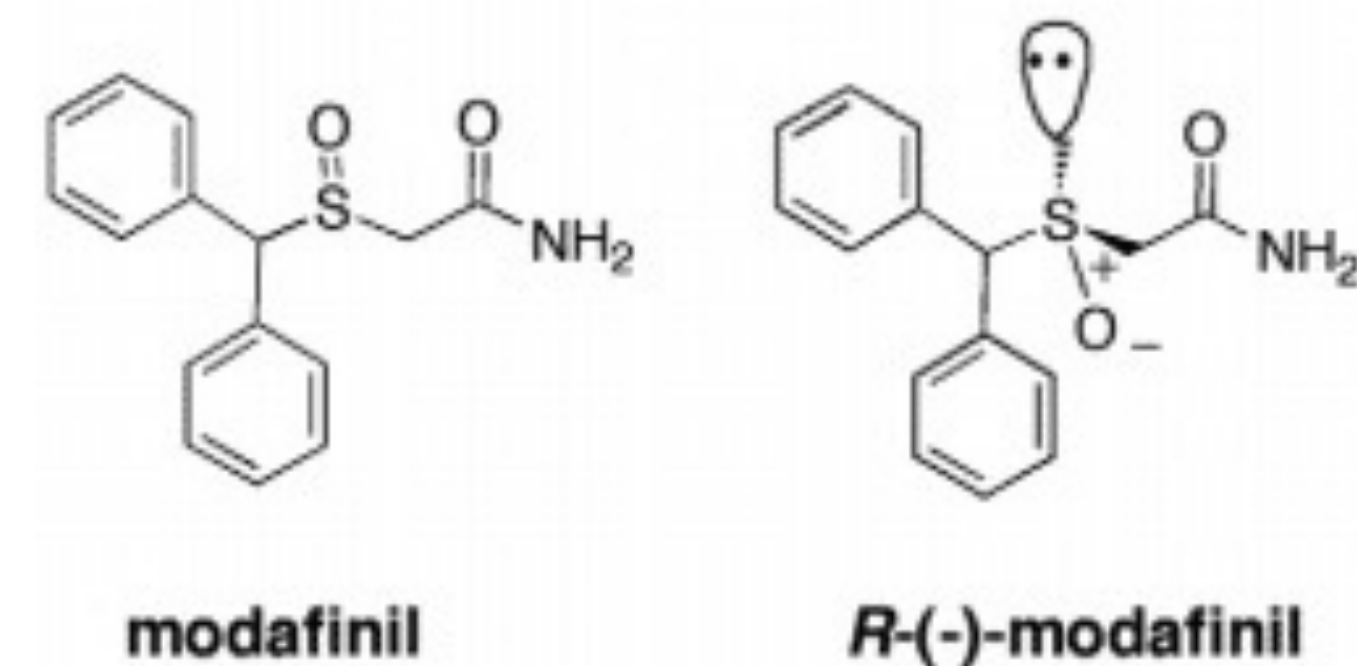
BACKGROUND

- Bipolar disorder is a severe and disabling chronic disease.
- While much attention has been paid to the treatment of the manic/hypomanic phases of bipolar disorder, bipolar depression consumes a larger portion of patients' lives and is less amenable to treatment.
- Growing interest has led to five drugs FDA-approved to treat bipolar depression:

Drug	Year approved
Olanzapine/fluoxetine combination	2003
Quetiapine	2006
Lurasidone	2013
Cariprazine	2019
Lumateperone	2021

Table 1: FDA-Approved Medications for Bipolar Depression

- For patients who do not respond to these medications or cannot access these medications, there has been growing interest in modafinil and armodafinil.
- Modafinil:** stimulant-like medication FDA-approved for narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. Thought to act on several neurotransmitters including dopamine, norepinephrine, serotonin, orexin and more.
- Armodafinil:** isolated R-enantiomer of modafinil.



- Five randomized controlled trials of modafinil and armodafinil have been conducted, three with a positive response^{1, 2, 3} and two with negative responses for efficacy^{4, 5}. Last two studies caused the sponsor to terminate these trials early. However, meta-analysis of all five showed significantly greater clinical response and remission of depression symptoms compared to placebo⁶.
- All dosages used in studies ranged from 100mg to 200mg.

CASE REPORT

- Pt: A 65 year old white female struggling with treatment-resistant bipolar depression since age 38.

History of Present Illness

- Depression symptoms: Anhedonia, low mood, guilt, increased sleep, decreased concentration, psychomotor retardation.
- Low suicidality
- Hypomanic symptoms: rapid speech, irritability, talkativeness
- No manic episodes
- Unable to work
- Comorbid anxiety

Family History

- Strong family history of depression
- Both parents
- Mother completed suicide
- Sibling with bipolar disorder

Medication History

- Fluoxetine produced 6-month remission, then relapsed. Continued taking fluoxetine after.
- Tried many other medications, no response.

Antidepressants

Citalopram
Fluoxetine
Sertraline
Paroxetine
Duloxetine
Venlafaxine
Tranylcypromine
Mirtazapine
Trazadone
Bupropion
Vilazodone

Ketamine

Mood stabilizers

Valproic acid
Lithium
Lamotrigine

Second-generation antipsychotics

Aripiprazole
Brexpiprazole
Olanzapine

Stimulants

Dextroamphetamine-amphetamine
Methylphenidate
Modafinil

Benzodiazepines

Clonazepam
Diazepam
Alprazolam

Neuromodulation

Electroconvulsive therapy (ECT)
Transcranial Magnetic Stimulation (TMS)

Table 2: Psychiatric Medications Failed by Patient with Treatment-Resistant Bipolar Depression

Armodafinil

- In 2016, an out-of-state psychiatrist prescribed her 250mg of armodafinil as adjunctive treatment, along with fluoxetine 40mg/day.
- Patient showed improvement.
- Drug was progressively titrated up to 500mg, 750 mg, and finally 1000 mg.
- Full remission of chronic depression
- Stable at current dose,
- Patient able to function, have a social life, began taking interest in new hobbies.
- In fall 2021, patient caught COVID-19 and began to have "Long Haul Covid" symptoms, including neurological symptoms, fatigue, progressive weakness.
- However, patient states armodafinil is alleviating most of her depressive symptoms, even in this situation.

CONCLUSION & DISCUSSION

- Adjunctive armodafinil is an innovative, currently off-label option for bipolar depression.
- This patient had persistent bipolar depression despite three courses of ECT, numerous TMS sessions, a trial of intravenous ketamine, and numerous trials of other medications, including two of the five FDA-approved options.
- Patient has not trialed the three more recent FDA-approved medications. However, given that she was stable on armodafinil, we felt it best to continue her current efficacious treatment.
- Tolerance is a potential cause for concern. This patient has been stable at 1000mg for three years without increases.
- Given that armodafinil and modafinil are stimulant-like, there is concern these drugs may induce manic symptoms. However, it has mania/hypomania and suicidal ideation have been shown to be low in randomized controlled trials in comparison to placebo⁶.
- Higher dosages of armodafinil should be considered for patients with treatment-resistant bipolar depression. It is possible at a higher dose a randomized controlled trial would show improved benefit.

Acknowledgements

Thank you to the patient who consented to have her case report published, in hopes that it would benefit others with bipolar depression.

References

- Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, Walden J, Leverich GS, Altshuler LL, Nakelsky S, Hwang S, Mintz J, Post RM. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry*. 2007;164(8):1242-9.
- Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry*. 2010;71(10):1363-1370.
- Calabrese JR, Frye MA, Yang R, Ketter TA; Armodafinil Treatment Trial Study N. Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled, multicenter trial. *J Clin Psychiatry*. 2014;75(10):1054-1061.
- Frye MA, Amchin J, Bauer M, Adler C, Yang R, Ketter TA. Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. *Int J Bipolar Disord*. 2015;3(1):18.
- Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder. *J Affect Disord*. 2015;181:87-91.
- Nunez NA, Singh B, Romo-Nava F, Joseph B, Veldic M, Cuellar-Barboza A, Cabello Arreola A, Vande Voort JL, Croarkin P, Moore KM, Biernacka J, McElroy SL, Frye MA. Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: A meta-analysis of randomized controlled trials. *Bipolar Disord*. 2020;22(2):109-120.

Contact kwokwy@mail.uc.edu with any questions!