Clinical and Practical **Psychopharmacology**

A Method for Deciding About the Possible Safety of Modafinil and Armodafinil in Patients With Seizure Disorder

Chittaranjan Andrade, MD

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

Modafinil or armodafinil (ar/mod) may be considered for patients with approved or unapproved indications, including excessive daytime drowsiness, fatigue, attention-deficit/hyperactivity disorder (ADHD), or addictions. Ar/mod is classified as a psychostimulant, and psychostimulants have been associated with a small risk of seizures. There is no guidance about the use of ar/mod in patients who are at risk of seizures. This article suggests how a physician may explore the safety of ar/mod if indicated in a patient at such risk. In summary, reading the prescribing information, writing to the drug manufacturer, and searching research databases suggest the following: Ar/mod and its metabolites and derivatives have dose-dependent anticonvulsant action in animal models; ar/mod is not associated with seizures as an adverse event in populations at risk, such as those with ADHD, head injury, and brain tumors; it is not associated with worsening of seizure disorder in patients with current seizure disorder; and it is not associated with seizures in overdose. These findings are reassuring. However, not all the data are of high quality, and potential ar/mod interactions with antiepileptic drugs (and other concurrent medications that affect the seizure threshold) need to be considered because ar/mod can induce the metabolism of some drugs and inhibit the metabolism of others. Decisions should be individualized, and decision-making should be a shared effort between patient and physician.

J Clin Psychiatry 2016;77(1):e25–e28
dx.doi.org/10.4088/JCP.15f10580

Clinical Question

Modafinil or its *R*-enantiomer armodafinil (ar/mod) may be considered for patients with approved or unapproved indications, including excessive daytime drowsiness, fatigue, attention-deficit/hyperactivity disorder (ADHD), or addictions. Ar/mod is generally classified as a psychostimulant.[1,2] Psychostimulants may be associated with seizures, even at therapeutic doses,[3] and some patients, such as those with ADHD, may be at higher risk of this psychostimulant-associated adverse effect.[4,5] So, is ar/mod associated with an increased risk of seizures? This question assumes importance when either of these drugs is considered indicated for a patient who has a current or past history of seizure disorder or who has risk factors for seizures (such as a past history of head injury or current treatment with a drug that lowers the seizure threshold).

Approaches

There is no formal guidance on the safety of ar/mod in patients with current or past history of seizure disorder or those with risk factors for seizures. This article therefore examines approaches to the situation. Direct approaches involve searching the prescribing information, checking electronic databases such as PubMed, and writing to the drug manufacturer for additional information. Indirect approaches involve examining the safety profile of the drug in vulnerable populations and in overdose. Animal data can provide specific clues about the effect of the drug on the seizure threshold. A tentative conclusion can be drawn from a synthesis of the information obtained.

Consulting the Prescribing Information

The first step is to consult the prescribing information, available from the manufacturer's website for each drug. There is no warning in the prescribing information regarding the use of either drug in seizure disorders, nor report of seizures as an adverse reaction at recommended doses or in overdose (this is easily determined by searching the prescribing information electronic documents for words such as *epilepsy, seizure,* and *fit*).

Writing to the Manufacturer

Official drug websites provide a manufacturer "Contact us" option with street address, e-mail address, and telephone numbers listed. The contact options and, indeed, the manufacturer identity could vary across countries and between generic and branded labels of a drug. Contacting one manufacturer of modafinil in November 2015 (with an inquiry about the safety of the drug in seizure disorders) elicited a swift response (within 24 hours) that listed the results of a PubMed search along with a statement that the manufacturer did not recommend the use of the drug beyond its FDA-approved product labeling. For armodafinil, the response to a similar inquiry was that there were no data on the subject from the clinical program and that the company was not aware of data on the subject in the published literature. Disappointingly, no unpublished data or "data on file" seemed available, such as information about the effect of ar/mod on the seizure threshold in animal studies.

Clinical Points

- In animal models, armodafinil and modafinil (ar/mod) and their metabolites and derivatives exert dose-dependent anticonvulsant action.
- In humans, there is no signal in the published literature for seizure risk with ar/mod. This conclusion is drawn from a survey of the literature on the use of ar/mod in patients with attention-deficit/hyperactivity disorder, head injury, brain tumors, and even seizure disorder. Modafinil overdose is also not associated with seizures.
- Ar/mod may increase or decrease the levels of certain antiepileptic drugs through pharmacokinetic drug interactions. These interactions need to be factored in when individualized and shared (between physician and patient) decisions are made.

Searching PubMed

PubMed is a service that is provided by the US National Library of Medicine. PubMed provides free access to MEDLINE, the NLM database of indexed citations and abstracts of medical, nursing, dental, veterinary, health care, and preclinical sciences journal articles. PubMed also includes certain life sciences journals that are not in MEDLINE.

A PubMed search conducted on December 3, 2015, using the search terms *modafinil* and *armodafinil* with *epilepsy, fit(s),* and *seizure(s)* identified fewer than 20 unique hits altogether, with only 4 animal studies[6–9] and 5 clinical reports[10–14] clearly relevant to the subject under consideration. These are examined in the sections that follow.

PubMed: The Animal Data

The earliest article, published in 2004,[6] reported that modafinil and its sulfone derivative protected against both maximal electroshock (MES) and pentylenetetrazol (PTZ)-induced seizures in mice and rats. A later study,[7] conducted in mice, found that modafinil (22.5, 45, and 90 mg/kg) decreased the incidence of hind limb tonic extension in an MES model and dose-dependently protected against PTZ-induced convulsions. In the megadose of 180 mg/kg, modafinil had antiseizure activity in the MES model but increased the seizure stage in the PTZ-kindling model.

A third study,[8] conducted in rats, found that 1 week of treatment with modafinil (1, 2, 4, 45, and 180 mg/kg/d) dose-dependently delayed the onset of the first myoclonic jerk and decreased the total major seizure period, but did not affect the latency to major seizure onset.

The last study[9] used electrically induced seizures in mouse and rat models to study the effects of modafinil (25–75 mg/d) and its metabolites on the anticonvulsant action of carbamazepine, phenobarbitone, phenytoin, and valproate. This study found that modafinil and its metabolites raised the threshold for convulsions. Modafinil and its metabolites also increased the anticonvulsant activity of carbamazepine, phenytoin, and valproate, but not phenobarbitone. Finally, modafinil and its metabolites raised total brain concentrations of carbamazepine and phenytoin, but did not alter concentrations of phenobarbitone and valproate.

In summary, the animal data suggest that modafinil and its metabolites dose-dependently exert anticonvulsant action in the standard (electroshock and chemical) models of epilepsy. This conclusion applies even to doses that are well above the usual human dose, per kg body weight The data are therefore reassuring in that they suggest that high doses of modafinil may protect against rather than predispose to seizures.

PubMed: The Clinical Data

Ivanenko et al[10] described a chart review of the use of modafinil in 13 children (mean age, 11 y) with excessive daytime somnolence. The mean dose of modafinil was 346 mg/d and the mean treatment period was 15.6 months. In this case series, a 2.5-year-old boy with a preexisting seizure disorder experienced a seizure after modafinil initiation. Sodium valproate was added, and there was no seizure recurrence despite continuation of modafinil.

Smith[11] reported the safe use of modafinil (300 mg/d) for >13 months in a patient with severe seizure disorder after stroke; the indication for modafinil was excessive daytime drowsiness and cognitive impairment associated with high doses of anticonvulsant medication (valproate, oxcarbazepine).

In a 10-year retrospective chart review, Artsy et al[12] identified 205 patients who were diagnosed with epilepsy and who were also receiving modafinil. Of these, 91 experienced further seizures while on modafinil and 114 did not. These 2 groups of patients did not differ significantly in age, gender, seizure etiology, or modafinil dose (about 200 mg/d). The effect of modafinil on seizure occurrence was no different in patients with symptomatic seizures versus those with idiopathic or cryptogenic epilepsy. Modafinil was discontinued in 6 patients due to concerns about possible seizure exacerbation. In 4 of these patients, however, discontinuation of modafinil did not much change the seizure history, suggesting that modafinil was not responsible for the exacerbation. One woman with glioblastoma had a first seizure a week after modafinil (200 mg/d) initiation. She was treated with low-dose levetiracetam; modafinil was continued, and the dose was actually raised, later, to 400 mg/d. There was no seizure recurrence until death, 6 months later. Three other patients had seizures 5–7 years after modafinil initiation. The authors concluded that, in the clinical setting, the use of modafinil does not appear to be associated with major exacerbation of seizures across a wide variety of neurologic disorders. They suggested that modafinil appears to be safe and may potentially be used in patients with epilepsy who also have fatigue or excessive daytime somnolence.[12] Garcia et al[13] viewed these findings and conclusions with enthusiasm but expressed a note of caution because the data[12] were retrospectively obtained.

The fifth and last PubMed paper[14] reviewed overdose data on drugs for ADHD. Seizure was not reported in association with modafinil overdose.

In summary, it appears that some patients with existing seizure disorder may experience seizures after starting

treatment with ar/mod; however, there is no clear indication that this is because of ar/mod as opposed to the existing seizure disorder.

Overdose

Drugs that lower the seizure threshold dose-dependently increase the risk of seizures; classical examples of drugs with this action are bupropion,[15] clomipramine,[16] and clozapine.[16] Many drugs that do not trigger seizures at therapeutic doses may do so in overdose; examples are citalopram,[17] escitalopram,[17] and vilazodone.[18] If modafinil carries a seizure risk, the overdose data could unmask the risk. So, what do the data show?

The highest overdose for modafinil reported in the prescribing information was 4,000–4,500 mg in adults and 50–63 mg/kg in a 3-year-old boy; this compares favorably with the recommended dose of 100–200 mg/d in adults. There was no report of seizures in association with modafinil overdose. The prescribing information contains no data on overdose with armodafinil.

A PubMed search conducted on December 4, 2015, identified 4 relevant articles for overdose with ar/mod. One[19] described 137 cases of modafinil overdose. A second[20] described a 15-year-old who overdosed with 5 g of modafinil. A third[21] reported supratherapeutic modafinil exposures in 87 subjects. None of these articles reported seizures as an adverse outcome. The last article, a review,[14] also did not report seizures with modafinil overdose even at the highest overdose of 8 g, that is, 40 times the (maximum) recommended dose.

Use in Populations Vulnerable to Seizures

Psychostimulant use may be associated with seizures in patients with ADHD.[4,5] However, modafinil has been safely administered to pediatric as well as adult patients with ADHD.[22–29] Patients with coarse brain disease are well known to be at increased risk of seizures. However, modafinil has been safely used in these populations, as well; the absence of seizures as an adverse event is especially noteworthy in patients with dementia,[30] head injury,[31,32] and brain tumors.[33,34]

The Importance of Drug Interactions

Modafinil induces the cytochrome P450 (CYP) enzymes 1A2 and 3A4; armodafinil induces CYP3A4.[35] Therefore, in patients with epilepsy, modafinil may reduce the blood levels and hence the efficacy of drugs metabolized by these enzymes. Antiepileptic drugs susceptible to this interaction include carbamazepine, clobazam, and others.[36] Modafinil and armodafinil also inhibit CYP2C9/19[37,38]; this can increase the levels and hence the efficacy (and adverse effects) of antiepileptic drugs metabolized by these enzymes. Susceptible drugs include phenobarbitone, primidone, phenytoin, and others.[36] Other common antiepileptic drugs such as valproate, lamotrigine, topiramate, gabapentin, and levetiracetam are probably little affected by ar/mod pharmacokinetic interactions.

Treatment Implications

Returning to the clinical question presented at the start of this article, it would seem that the following conclusions can reasonably be drawn:

1. Animal data suggest that ar/mod has dose-dependent anticonvulsant action.
2. Clinical data suggest that ar/mod is not associated with an increased risk of seizures even in overdose, even in neurologically vulnerable patients such as those with head injury, and even in patients with epilepsy. However, the most important data (addressing patients with epilepsy) are limited, uncontrolled, observational, and mostly retrospective. Additionally, patients with epilepsy and serious head injury would almost certainly have been protected with antiepileptic medications.
3. The potential for ar/mod-related induction or inhibition of ongoing antiepileptic medication (if any), or ongoing treatment with any other drug that influences the seizure threshold, must be factored into decision-making processes.

Decision-making in all branches of medicine is based on individualized risk-benefit ratios. Although the results of this review suggest that the risk of seizure with ar/mod is low, risk cannot be ruled out altogether. The physician and client therefore need to look at the evidence presented and jointly decide whether the expected benefit with ar/mod treatment overrides the potential risk before treatment with ar/mod is initiated.

Parting Notes

Enthusiastic physicians may want to search research databases beyond PubMed; this is applaudable because PubMed searches do not identify all eligible articles, even those from within the PubMed database itself. Searches can also be conducted in clinical trial registries; investigators of completed but unpublished studies can be contacted for information about seizures as an adverse event. Broader search results can be obtained from more general search engines such as Google Scholar and even Google. Many of the identified links will offer data collected without scientific rigor, personal experiences reported by patients, and educated (or not) opinions. The reader will need to use discretion in applying information from such sources in decision-making processes.

As a final remark, the earliest reference to modafinil appeared in PubMed in 1986. After nearly 3 decades of availability, it is reassuring that there is no signal in the published literature suggesting risk in patients with seizure disorder. This suggests that there may not be a risk, or if a risk truly exists, it must be small.

REFERENCES

1. Wood S, Sage JR, Shuman T, et al. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. *Pharmacol Rev.* 2014;66(1):193–221.
2. Lindenmayer JP, Nasrallah H, Pucci M, et al. A systematic review of

psychostimulant treatment of negative symptoms of schizophrenia: challenges and therapeutic opportunities. *Schizophr Res*. 2013;147(2–3):241–252.
3. Zagnoni PG, Albano C. Psychostimulants and epilepsy. *Epilepsia*. 2002;43(suppl 2):28–31.
4. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. *CNS Drugs*. 2008;22(3):213–237.
5. Cortese S, Holtmann M, Banaschewski T, et al; European ADHD Guidelines Group. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry*. 2013;54(3):227–246.
6. Chatterjie N, Stables JP, Wang H, et al. Anti-narcoleptic agent modafinil and its sulfone: a novel facile synthesis and potential anti-epileptic activity. *Neurochem Res*. 2004;29(8):1481–1486.
7. Chen CR, Qu WM, Qiu MH, et al. Modafinil exerts a dose-dependent antiepileptic effect mediated by adrenergic alpha1 and histaminergic H1 receptors in mice. *Neuropharmacology*. 2007;53(4):534–541.
8. Ozsoy S, Aydin D, Ekici F. Effects of modafinil on pentylenetetrazol-induced convulsive epilepsy. *Bratisl Lek Listy (Tlacene Vyd)*. 2015;116(3):162–166.
9. Zolkowska D, Andres-Mach M, Prisinzano TE, et al. Modafinil and its metabolites enhance the anticonvulsant action of classical antiepileptic drugs in the mouse maximal electroshock-induced seizure model. *Psychopharmacology (Berl)*. 2015;232(14):2463–2479.
10. Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. *Sleep Med*. 2003;4(6):579–582.
11. Smith BW. Modafinil for treatment of cognitive side effects of antiepileptic drugs in a patient with seizures and stroke. *Epilepsy Behav*. 2003;4(3):352–353.
12. Artsy E, McCarthy DC, Hurwitz S, et al. Use of modafinil in patients with epilepsy. *Epilepsy Behav*. 2012;23(4):405–408.
13. Garcia VA, Matos G, Tufik S, et al. Demystifying the effect of modafinil in epilepsy. *Epilepsy Behav*. 2012;24(2):287.
14. Spiller HA, Hays HL, Aleguas A Jr. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. *CNS Drugs*. 2013;27(7):531–543.
15. Ross S, Williams D. Bupropion: risks and benefits. *Expert Opin Drug Saf*. 2005;4(6):995–1003.
16. Pisani F, Oteri G, Costa C, et al. Effects of psychotropic drugs on seizure threshold. *Drug Saf*. 2002;25(2):91–110.
17. Yilmaz Z, Ceschi A, Rauber-Lüthy C, et al. Escitalopram causes fewer seizures in human overdose than citalopram. *Clin Toxicol (Phila)*. 2010;48(3):207–212.
18. Acker EC, Sinclair EA, Beardsley AL, et al. Acute vilazodone toxicity in a pediatric patient. *J Emerg Med*. 2015;49(3):284–286.
19. Spiller HA, Borys D, Griffith JR, et al. Toxicity from modafinil ingestion. *Clin Toxicol (Phila)*. 2009;47(2):153–156.
20. Neuman G, Shehadeh N, Pillar G. Unsuccessful suicide attempt of a 15 year old adolescent with ingestion of 5000 mg modafinil. *J Clin Sleep Med*. 2009;5(4):372–373.
21. Carstairs SD, Urquhart A, Hoffman J, et al. A retrospective review of supratherapeutic modafinil exposures. *J Med Toxicol*. 2010;6(3):307–310.
22. Biederman J, Swanson JM, Wigal SB, et al. 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. *Pediatrics*. 2005;116(6):e777–e784.
23. Swanson JM, Greenhill LL, Lopez FA, et al. 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. *J Clin Psychiatry*. 2006;67(1):137–147.
24. Greenhill LL, Biederman J, Boellner SW, et al. A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45(5):503–511.
25. Biederman J, Swanson JM, Wigal SB, et al; Modafinil ADHD Study Group. 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. *J Clin Psychiatry*. 2006;67(5):727–735.
26. Boellner SW, Earl CQ, Arora S. Modafinil in children and adolescents with attention-deficit/hyperactivity disorder: a preliminary 8-week, open-label study. *Curr Med Res Opin*. 2006;22(12):2457–2465.
27. Amiri S, Mohammadi MR, Mohammadi M, et al. Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(1):145–149.
28. Kahbazi M, Ghoreishi A, Rahiminejad F, et al. A randomized, double-blind and placebo-controlled trial of modafinil in children and adolescents with attention deficit and hyperactivity disorder. *Psychiatry Res*. 2009;168(3):234–237.
29. Arnold VK, Feifel D, Earl CQ, et al. A 9-week, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study to evaluate the efficacy and safety of modafinil as treatment for adults with ADHD. *J Atten Disord*. 2014;18(2):133–144.
30. Frakey LL, Salloway S, Buelow M, et al. A randomized, double-blind, placebo-controlled trial of modafinil for the treatment of apathy in individuals with mild-to-moderate Alzheimer's disease. *J Clin Psychiatry*. 2012;73(6):796–801.
31. Jha A, Weintraub A, Allshouse A, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil*. 2008;23(1):52–63.
32. Kaiser PR, Valko PO, Werth E, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology*. 2010;75(20):1780–1785.
33. Gehring K, Patwardhan SY, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neurooncol*. 2012;107(1):165–174.
34. Boele FW, Douw L, de Groot M, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. *Neuro-oncol*. 2013;15(10):1420–1428.
35. Andrade C. Modafinil and armodafinil in schizophrenia. *J Clin Psychiatry*. 2012;73(8):e1062–e1064.
36. de Leon J. The effects of antiepileptic inducers in neuropsychopharmacology, a neglected issue, part I: a summary of the current state for clinicians. *Rev Psiquiatr Salud Ment*. 2015;8(2):97–115.
37. Robertson P Jr, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet*. 2003;42(2):123–137.
38. Darwish M, Kirby M, Robertson P Jr, et al. Interaction profile of armodafinil with medications metabolized by cytochrome P450 enzymes 1A2, 3A4 and 2C19 in healthy subjects. *Clin Pharmacokinet*. 2008;47(1):61–74.