PharmaNote®

VOLUME 28, ISSUE 8 MAY 2013

OFF-LABEL USE OF MODAFINIL IN DEPRESSION

Erika Walters, Pharm.D.

Modafinil is a novel wakefulness-promoting agent approved by the Food and Drug Administration (FDA) for use in narcolepsy, shift-work disorder, and sleep apnea.[1] Since 1998, it has been marketed in the U.S. under the brand name Provigil® (Cephalon, Inc.).[1,2] In 2011, the first generic formulation was approved.[3,4] Modafinil is used to improve wakefulness and alertness and to reduce excessive daytime sleepiness (EDS) and fatigue.[5-7] It works differently than other central nervous system (CNS) stimulants and is believed to have a lower risk of tolerance, dependence and systemic side effects.[5,6] Available evidence indicates that modafinil is safe and well-tolerated. For more than a decade, it has been studied in other conditions such as cancer fatigue, Parkinson's disease, myotonic dystrophy, post-surgical anesthesia, attention deficit hyperactivity disorder, depression, cocaine dependence, schizophrenia, and cerebral palsy.[5,6]

Much research has aimed to identify the utility of modafinil in the treatment of depression. Major depressive disorder (MDD) has an estimated lifetime prevalence of 1 in 6 Americans and frequently includes fatigue as a core symptom.[8,9] Researchers hoped that modafinil would improve symptoms of depression either directly by improving response to antidepressant therapy or indirectly by offsetting the sedation associated with antidepressant therapy.[6,7] Several small, open-label trials have suggested a possible benefit of modafinil in depression[10-14] but these benefits have not been replicated in double-blind, placebo-controlled trials conducted to date.[6,7,14] Larger clinical trials are needed to determine the efficacy of modafinil in the treatment of depression and to identify the subgroups and clinical scenarios in which benefit is expected. Based on the limited evidence from randomized controlled trials, practice guidelines issued by the American Psychiatric Association (APA) for the treatment of MDD state that modafinil may be recommended to augment antidepressant therapy in patients with persistent fatigue or hypersomnolence.[9] This was given a grade III recommendation meaning modafinil may be recommended on the basis of individual circumstances, since current evidence is insufficient to recommend its routine use.[9]

Until such trial data are available, modafinil is prescribed off-label for the treatment of MDD when the potential benefits outweigh the risks of its use.[15] The off-label prescribing of modafinil is expected to increase since the recent approval of a generic formulation will lower the cost of modafinil. Before prescribing modafinil in depression, providers should understand the current evidence about its efficacy and safety.

This article will summarize safety information about modafinil and review the available literature regarding its use in MDD.

PHARMACOLOGY & PHARMACOKINETICS

Like other CNS stimulants, modafinil reduces fatigue and EDS and improves mood and daytime per-

INSIDE THIS ISSUE:

formance.[6] Its mechanism of action remains unclear. Initially, it was believed to inhibit reuptake of dopamine in regions of the brain responsible for alertness.[16] Animal studies have shown that modafinil decreases levels of GABA in several regions of the brain while increasing levels of glutamate and serotonin in other regions.[7] More recently, it was identified as an agonist of hypocretin-orexin receptors.[13,17] A combination of mechanisms may be responsible for the therapeutic effects of modafinil. The way modafinil works to improve fatigue may be different from the way it improves depression.

Modafinil works differently than conventional stimulants such as amphetamines and methylphenidate. Conventional stimulants are associated with large increases in neurogenic amines throughout the brain.[7] Side effects include tachycardia, hypertension, insomnia, depression and paranoia.[18] In addition, conventional stimulants have a high risk of dependence, tolerance and abuse.[19] In the U.S., they are Schedule II (C-II) controlled substances due to a well-established potential for abuse.

By comparison, modafinil causes much smaller changes in neurotransmitter levels in fewer regions of the brain.[7] As a result, central and cardiovascular side effects are generally mild.[2,19] Its effects on sleep are dose-dependent at a dose range of 100 mg to 600 mg daily.[19] Its effects have been compared to a long-acting caffeine[20] and it has not been linked to withdrawal, tolerance, or rebound insomnia.[5,7] It is classified as a Schedule IV (C-IV) controlled substance.

Modafinil is a racemic substance which is orally absorbed. It reaches peak plasma concentrations in 2 to 4 hours and has a half-life of 15 hours.[2] Modafinil undergoes hepatic metabolism via the cytochrome P-450 (CYP) enzyme system. It is a known substrate of CYP3A4 and a known inducer of CYP3A4/5 and CYP1A2 in humans.[21] In vitro studies suggest that it inhibits activity of CYP2C9 and CYP2C19.[7] The majority is renally excreted in the form of two inactive metabolites.[1,2,7]

Clinical Trials in Depression

For more than 10 years, researchers have studied the effects of modafinil in patients meeting criteria for MDD set out in the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition. Numerous retrospective studies and small, prospective trials have indicated a link between modafinil and improvements in symptoms of depression.[7] Weaknesses of these trials include small sample size, open-label design, lack of a comparator group, and short-term follow-up. In order to identify a causal relationship between modafinil and improvement in depression several prospective, randomized, placebo-controlled trials have been conducted. Modafinil has been studied as monotherapy and as adjunctive therapy to standard antidepressant agents at a variety of doses for different durations. Four of the largest prospective, controlled trials examining the role of modafinil in MDD are summarized below (**Table 1**).

Two double-blind, placebo-controlled trials were conducted by DeBattista et al.[22] and Fava et al.[23] Both evaluated the effect of modafinil on symptoms of depression in patients who had achieved a partial response to an adequate trial of antidepressant therapy (more than 4 weeks of therapy) and reported persistent fatigue or sleepiness. In addition to ongoing antidepressant therapy, participants were randomized to receive either modafinil or placebo as an augmentation agent.

Patients enrolled in the study by DeBattista et al. spent at least 6 weeks immediately prior to enrollment on a stable dose of antidepressant therapy.[22] Pretreatment therapy was continued during the trial in both groups. A majority of patients reported fatigue (82%) and half reported excessive sleepiness (51%). Patients could be on multiple antidepressants prior to enrollment but their antidepressant therapy did not change after enrollment; 7% used more than one antidepressant. After randomization to placebo (N= 67) or modafinil (N= 69) doses ranged from 100 to 400 mg daily depending on patient response and tolerability.[22]

Fava et al. used a similar study design to evaluate a more well-defined sample.[23] Enrollees in this trial were required to have achieved a partial response from 8 weeks of monotherapy with a selective serotonin reuptake inhibitor (SSRI). All reported persistent fatigue. Patients completed a single-blind, placebo run-in before randomization to either placebo (N= 153) or modafinil (N= 158) for 8 weeks. Participants in both groups continued their pretreatment SSRI.[23]

In both of these studies, efficacy was evaluated with a combination of instruments.[7] The Hamilton Rating Scale for Depression (HAM-D) 17-Item Survey (HAM-D-17), HAM-D-21 and HAM-D-31 were used to assess depression. The Clinical Global Impression of Change (CGI), Montgomery–Asberg Depression Rating Scale (MADRS) and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) evaluated quality of life. The Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS) and the Epworth Sleepiness Scale (ESS) measured fatigue and sleepiness.

In both trials, both groups experienced significant improvements in symptoms of depression, fatigue and sleepiness.[22,23] DeBattista and colleagues observed similar reductions in scores on the HAM-D-17 and

Table 1 | Summary of clinical trials evaluating modafinil in depression

Trial	Design	Sample Size	Outcome measures	Results
DeBattista, 2003[22]	• 6-wk • Partial response to AD after at least 6-wk of treatment with AD • RCT, DB, PC, MC • Modafinil 100-400 mg/day	N = 69 M (87% comp) N= 67 P	Depression (HAM-D), Fatigue (FSS), Sleepiness (ESS), Global function (CGI-C, SF-36).	• Significant placebo effect • M had significantly > improvements in FSS scores at wk 2; ($p < .05$) and sleepiness ESS scores at wk 1 ($p < .01$) from baseline; no differences at wk 6 • No significant differences (HAM-D, CGI-C, and SF-36) in M vs P
Fava, 2005[23]	• 8 wk • Adjunctive therapy for patients without complete response to AD • No comparator • Modafinil 200 mg/day	N= 158 M (85% comp) N= 153 P	Fatigue (BFI, FSS)	• Changes in BFI and FSS scored similar to placebo • CGI-I scores improved significantly with M compared to P at wk 1 $p = 0.049$ and at final visit $p = 0.01$
Dunlop, 2007[24]	• Phase 1: 6 wk • RCT, DB, MC of open-label SSRI combined with DB addition of M or P • Phase 2: 4 wk • Extension study combined open-label M to SSRI	N= 37 SSRI + M (76% comp) N= 36 SSRI + P (75% comp)	Mixed-model analysis of change in sleepiness (ESS) and depression (31-item HAM-D)	• No difference between M and P on EPS • M improved hypersomnia items on 31-item HAM-D • *Trial discontinued early due to suicidal ideation in 2 M users
Vaishnavi, 2006[25]	• 12 wk • monotherapy for atypical depression • DB, PC, relapse prevention trial after 12 wk open-label treatment with M •	N= 24 M (92% comp) N=26 P (73% comp)	Depression (29-item HAM-D)	• M reduced HAM-D from baseline ($P < 0.0001$), • Benefits were maintained in both arms during DB continuation phase ($P = 0.92$)

Abbreviations: *AD = antidepressant; BFI= Brief Fatigue Inventory; CGI-C= Clinical Global Impression of Change; comp= completed; DB = double-blind; ESS= Epworth Sleepiness Scale; FSS= Fatigue Severity Scale; HAM-D= Hamilton Rating Scale for Depression; M= modafinil; MC = multicenter; NSS= nonstatistically significant; P= placebo; PC = placebo-controlled; RCT= randomized controlled trial; SF-36= Medical Outcomes Study 36-Item Short-Form Health Survey; SIGH-D= Structured Interview Guide For The Hamilton Depression Rating Scale; SS= statistically significant; SSRI = selective serotonin reuptake inhibitor; wk = week

HAM-D-21 from baseline to final visit in groups randomized to placebo and modafinil. Modafinil did not improve CGI-C or SF36 when compared to placebo.[22] Similarly, Fava et al. found no difference between groups on measures of HAM-D-31 and HAM-D-17 or the BFI or MADRS.[23]

Fava et al. did identify several differences favoring use of modafinil. Modafinil was associated with improvements in CGI-C scores of global functioning which were significantly greater than placebo at week 1 (p= 0.049) and the final study visit (p= 0.01). Modafinil was also associated with a significantly higher proportion of patients reporting at least minimal benefit from therapy (70%) versus placebo (53%; p = 0.006) and nonsignificantly higher proportion of responders (reporting much or very much improved symptoms). A post hoc subgroup analysis of patients with baseline HAM-D scores ≥14, ESS scores changed more with modafinil users (4.0 +/- 4.9) than in placebo users (3.0 +/- 4.1) (p= 0.03).[23] However, this subgroup was not pre-specified and the analysis was criticized for failure to use a correction factor for multiple comparisons.[7,14] After 8 weeks, modafinil had significantly greater improvements in CGI-C scores (p= 0.02) for overall clinical condition and significantly greater reductions in BFI scores for worst fatigue (p< 0.05) when compared to placebo.[23]

Notably, modafinil was well-tolerated with a variety of antidepressants. No significant safety issues were identified. Only headaches, nervousness, nausea, jitteriness and weight loss were reported significantly more often in groups receiving modafinil.[22,23] Authors concluded that modafinil may be a useful adjunct therapy for short-term management of fatigue and sleepiness in patients who are partial responders to antidepressant therapy.[22,23]

In a third randomized controlled trial, modafinil was studied as an adjunct to antidepressants, initiated at the onset of antidepressant therapy rather than several weeks later.[24] Dunlop et al. designed this double-

blind, placebo-controlled study to test the hypothesis that modafinil would improve symptoms during the period of six to eight weeks of antidepressant therapy before antidepressants achieved their full therapeutic effects.[24] During this lag period, side effects including sedation are reported at their highest rates.[7]

During phase 1 of the study, patients initiated antidepressant treatment with an open-label SSRI plus either placebo or modafinil (N= 36) for 6 weeks. Doses of modafinil ranged from 100 mg to 200 mg daily. In phase 2, open-label modafinil was used as an adjunct to an SSRI for 4 weeks.

The study was designed to compare the impact of modafinil when it was used at different times during therapy. Researchers hypothesized that modafinil would counteract the sedation which is frequently reported side effect of antidepressant therapy. This should improve tolerability of antidepressant therapy and increasing the proportion of participants who use their antidepressant for the 8 weeks required for SRIs to achieve their full therapeutic effects.

The study was planned for 10 weeks but was terminated early due to development of suicidal ideation in two participants in the modafinil arm. Only 51 of 73 (70%) of enrollees completed the study. During the study period, modafinil and was no different than placebo on the primary outcome, rate of change in sleepiness scores as measured by the ESS. Premature discontinuation of the trial reduced the power to detect a difference between modafinil and placebo.

After 5 weeks, groups had similar proportion of patients achieving a 50% reduction in HAM-D-31 (M= 78%, P= 69%, chi squared= 0.8), had similar MADRS scores (M= 75%, P= 86%, chi squared= 0.14) and similar ESS scores. Remission rates were no different between groups. In both groups, there were early indications of improvements in sleepiness (ESS) and fatigue (FSS) which were not sustained.[24]

These authors concluded that on the basis of secondary endpoints, modafinil showed some evidence of superiority over placebo. They recommended further study in order to identify who stands to benefit most from modafinil.[24]

The fourth prospective, randomized clinical trial Vaishnavi et al. also identified some benefit of modafinil in patients with atypical depression characterized by hypersomnia.[9,25] Over 12 weeks of open-label treatment, modafinil significantly improved mean HAM-D scale scores (P< 0.001). These benefits were sustained in the both modafinil and placebo arms during the double-blind, placebo-controlled, continuation phase (p= 0.92).[2]

Adverse Effects, Contraindications, Interactions, & Special Populations

Modafinil is generally well-tolerated.[6,7,15] Its common side effects include headache and nausea (**Table 2**). Serious side effects may include Stevens-Johnson Syndrome, toxic epidermal necrosis, drug rash with Eosinophilia and Systemic Symptoms, psychiatric symptoms, and hypersensitivity reactions including angioedema.[7]

Long-term safety data is lacking. Safety and efficacy have not been established in pregnant women, in patients less than 17 years of age, or in geriatric patients. It should be used cautiously in pediatric patients, due to concern over possible cardiovascular side effects from stimulants and higher incidence of dermatologic reactions in children.[7, 26]

Dose adjustment is advised in patients with low body weight and severe hepatic impairment.[2,3] Due to the risk of accumulation of metabolites, modafinil is not recommended in renal dysfunction.

Contraindications include left ventricular hypertrophy or symptomatic mitral valve prolapse, history of myocardial infarction, hypertension, psychosis or severe liver dysfunction and concomitant use of other CNS stimulants.[3]

Numerous drug-drug interactions are possible.[1,2]

Table 2 | Adverse effects of modafinil [3]

	Modaf (%) n = 934	Placebo (%) n = 567	
Headache	34	23	Dose related
Back Pain	6	5	
Flu Syndrome	4	3	
Chest Pain	3	1	
Hypertension	3	1	
Nausea	11	13	
Diarrhea	6	5	
Dyspepsia	5	4	
Dry Mouth	4	2	
Anorexia	4	1	
Rhinitis	7	6	
Pharyngitis	4	2	
Insomnia	5	1	
Anxiety	5	1	Dose related
Dizziness	5	4	
Nervousness	7	3	

Modaf= modafinil

Modafinil is a substrate of CYP 3A4, a moderate inducer of CYP1A2, CYP2D6, and CYP3A4/5, a weak inhibitor of CYP2C9 and a strong inhibitor of CYP2C19.[7] As a CYP3A4/5 substrate, modafinil is vulnerable to drug-drug interactions with numerous CYP3A4 inducers and inhibitors which have the potential to decrease or increase serum levels of modafinil.[17] In vitro studies indicate induction of CYP1A2, CYP2D6, and CYP3A4/5 (moderate) by modafinil, which may decrease concentrations and decrease effectiveness of medications including steroidal contraceptives, cyclosporine and triazolam.
[3,7] Inhibition of CYP2C9 and CYP2C19 may increase concentrations of medications including warfarin, phenytoin, losartan, sulfamethaxazole, and torsemide.[3,7]

The abuse potential of modafinil is less than other stimulants used to promote wakefulness such as amphetamines (C-II) or methylphenidate (C-II). Modafinil has not been associated with withdrawal symptoms or rebound hypersomnolence after abrupt discontinuation. At usual doses, it has not been associated with development of tolerance.

Implications for Clinical Practice

A number of small, open-label studies have shown benefits of modafinil on fatigue, daytime sleepiness and symptoms of depression. In these studies, modafinil has been used at doses similar to those used in treatment of narcolepsy, shift-work disorder and sleep apnea. It has been well-tolerated with a variety of antidepressants. Rarely, serious cardiovascular and dermatologic reactions may occur. Numerous medications may have clinically significant drug interactions with modafinil.

Evidence from prospective, placebo-controlled trials indicates that there is a modest, short-term benefit of modafinil in patients with MDD. However, larger studies are needed to evaluate the benefit of modafinil in different subtypes of depression and in different patient populations. These studies will provide valuable information about the clinical scenarios in which modafinil is most likely to offer benefit.

Based on available evidence, APA guidelines for MDD state that modafinil may be reasonable agent to augment antidepressant therapy in patients who report residual fatigue or hypersomnia. However, this was a grade III recommendation because of the limited evidence available from randomized clinical trials. The appropriate dose and duration of therapy for this indication remain uncertain. Guidelines highlight the need for further research.

Summary

Modafinil is a novel wakefulness-promoting agent FDA-approved for use in narcolepsy, sleep apnea and shift-work disorder. Compared to other CNS stimulants, it has a lower risk of serious systemic side effects and a lower potential for abuse. Since its approval in the U.S. in 1998, it has been studied in a number of disease states and has been widely prescribed off-label. Small, open-label studies have suggested a benefit of modafinil in the treatment of MDD but results from larger, randomized controlled trials have not produced clear or consistent evidence of efficacy. More studies are needed to assess the effects of modafinil in patients with depression and to determine the role in therapy. Until more data is available, treatment guidelines indicate that in certain clinical scenarios, modafinil may be reasonable agent in the treatment of resistant depression with residual fatigue. The recent approval of a generic formulation may lead to an increase in off-label prescribing of modafinil for treatment of depression. Providers should be aware that there is no convincing evidence of its efficacy in the treatment of depression. Rare but serious cardiovascular and dermatologic side effects are possible, and a number of drug-drug interactions are likely.

References

1. Modafinil. LexiDrugs System. Hudson, OH: Lexi-Comp, expires 2013 Dec 31 (accessed 2013 Jan 11).
2. Product information. Provigil (modafinil). Frazer, PA. Cephalon Inc., August 2007.
3. Webber KO. From the director. Presented at: GPhA Fall Technical Meeting, North Bethesda, MD, ST, October 5, 2011.
4. Food and Drug Administration. First-Time Generic Drug Approvals - July 2012. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm330400.htm. (accessed 2013 Jan 1).
5. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000;54: 1166-75.
6. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. J Clin Psychiatry 2006;67:554-66.
7. Kumar R. Approved and investigational uses of

modafinil: an evidence-based review. Drugs. 2008;68:1803-39.
8. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005;62:1097–1106.
9. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010.
10. Konuk N, Astoy N, Atik L, Akay O. Open-label study of adjunct modafinil for the treatment of patients with fatigue, sleepiness, and major depression treated with selective serotonin reuptake inhibitors. Adv Ther 2006;23:646-54.
11. Thase ME, Fava M, DeBattista C, Arora S, Hughes RJ. Modafinil augmentation of SSRI therapy in patients with major depressive disorder and excessive sleepiness and fatigue: a 12-week, open-label, extension study. CNS Spectr 2006;11:93-102.
12. Ninan PT, Hassman HA, Glass SJ, McManus FC. Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue. J Clin Psychiatry 2004;65:414-20.
13. Schwartz TL, Azhar N, Cole K, et al. An open-label study of adjunctive modafinil in patients with sedation related to serotonergic antidepressant therapy. J Clin Psychiatry 2004;65:1223-7.
14. Lam JY, Freeman MK, Cates ME. Modafinil augmentation for residual symptoms of fatigue in patients with a partial response to antidepressants. Ann Pharmacother 2007;41:1005-12.
15. Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balken TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology 2002;159:238–247.
16. Wisora JP, Eriksson KS. Dopaminergic—adrenergic interactions in the wake promoting mechanism of modafinil. Neuroscience 2005:132:1027–1034.
17. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, et al. Narcolepsy in orexin Knockout Mice: Molecular Genetics of Sleep Regulation Cell 1999;98:437–51.
18. Westfall TC, Westfall DP. Adrenergic Agonists and Antagonists. In: Chabner BA, Brunton LL, Knollmann BC, eds. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12nd ed. New York: McGraw-Hill, 2011. http://www.accesspharmacy.com/content.aspx?aID=16661344. Accessed January 12, 2013.
19. Dopp JM. Sleep Disorders. In: Talbert RL, DiPiro JT, Matzke GR, Posey LM, Wells BG, Yee GC, eds. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York: McGraw-Hill, 2011. http://www.accesspharmacy.com/content.aspx?aID=7990389. Accessed January 12, 2013.
20. Wesensten NJ, Belenky G,Thorne DR, Kautz MA, Balkin TJ. Modafinil vs. Caffeine: Effects on Fatigue During Sleep Deprivation. Aviation, Space, and Environmental Medicine 2004;75:520-526.
21. Robertson P, DeCory HH, Madan A, Parkinson A. In vitro inhibition and induction of human hepatic cytochrome P450 enzymes by modafinil. Drug Metab Dispos 2000;28:664–671.
22. DeBattista C, Doghramji K, Menza MA, Rosenthal MH, et al. Modafinil in Depression Study Group. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 2003;64 1057-64.
23. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to SSRIs with persistent fatigue and sleepiness. J Clin Psychiatry 2005;66:85-93.
24. Dunlop BW, Crits-Christoph P, Evans DL, Hirschowitz J, et al. Coadministration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. J Clin Psychopharmacol 2007;27:614–9.
25. Vaishnavi S, Gadde K, Alamy S, Zhang W, et al. Modafinil for atypical depression: effects of open-label and double-blind discontinuation treatment. J Clin Psychopharmacol 2006;26:373-8.
26. Vetter VL, Elia J, Erickson CH, et al. Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation 2008;117:2407-23.
27. Robertson Jr P, Hellriegel ET, Arora S, et al. Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. Clin Pharmacol Ther 2002;71:46-56.

Clinical Trial Update

Statin rechallenge following discontinuation—Statins have been shown to improve mortality in patients with cardiovascular (CV) disease and are recommended by numerous guidelines for primary and secondary prevention of CV events. However, statins are often discontinued due to side effects and may not be restarted. Most commonly patients experience myalgias or myopathy while few have CK elevations, rarely progressing to rhabdomyolysis. As statins represent first-line treatment options for CV disease, permanent discontinuation may lead to suboptimal management and an increased risk for future CV events. However, rechallenging with a statin following a statin-related adverse event (AE) is controversial.

Zhang and colleagues[1] performed a retrospective analysis of two large hospitals based in Boston, Massachusetts to determine the rate of statin discontinuation due to AEs as well as the rate of successful rechallenge. The investigators identified patients with a prescription for a statin from January 1, 2000 to December 31, 2008. Information about statin-related events was identified using electronic medical record (EMR) data as well as computer processing programs which evaluated narrative provider notes within the EMR. Statin discontinuation was identified by documentation in the EMR associated with a discontinued prescription (requiring a reason for discontinuation, "structured EMR data"), provider documentation in encounter notes, or the absence of a statin prescription for 12 months in the EMR.

A total of 107,835 patients were included in the analysis. Over 50% of the study patients had their statin discontinued at least once; adverse reaction was noted as the reason for discontinuation for only 2233 patients in the structured EMR data.

Statin-related AEs were identified in 18,778 patients (17.4%), with myalgia or myopathy being the most commonly identified event and being noted in 4.7% of the total study population and in 27% of patients who had any statin-related event documented. Notably, rhabdomyolysis and memory problems were only reported in 0.006% and 0.06% of patients, respectively.

Within the subgroup of patients identified as having a statin-related event (n=18,778), over 59% (n=11,124) had the statin temporarily discontinued. Over half of these patients (n=6579) were rechallenged with a statin over the next 12 months and 90% (n=6064) were taking a statin 12 months after the original statin-related event. Of those that were rechallenged with the same statin (n=2721) nearly half were able to continue the statin following the rechallenge (n=1295). A second statin-related event was documented in only 13% (n=510) of those who were rechallenged following the original statin-related event. Patients who were rechallenged were less likely to have CK elevations compared to those who were not rechallenged.

The study is not without limitations. As it is retrospective, only associations could be established. The structured EMR data may not have accurately identified true reasons for discontinuation and incomplete documentation may have limited identification of all statin-related events.

However, the analysis indicates that most patients who discontinue a statin due to stain-related AEs may be successfully rechallenged. Given the well documented efficacy of statins, rechallenge should likely be considered for those reporting statin-related AEs as a reason for discontinuation.

1. Zhang H, Plutzky J, Skentzos, S, et al. Discontinuation of statins in routine care settings. Ann Intern Med 2013;158:526-34.

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
University of Florida