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Conflict of Interest Disclosures: None reported.
Funding/Support: The research reported herein was supported by the Department of Veterans Affairs National Center for Patient Safety, a National Institutes of Health K23 career development award (K23CA125585) to Dr Singh and in part by the Houston VA Health Services Research and Development Center of Excellence (HFP90-020). Dr Sittig is supported in part by a SHARP contract from the Office of the National Coordinator for Health Information Technology (ONC No. 10510592).
Additional Contributions: We thank additional members of our project team, Donna Espadas, BS; Daniel Murphy, MD, MBA; Michael Smith, PhD; and Archana Laxmisan, MD, MA (all affiliated with the Houston VA Health Services Research and Development Center of Excellence), for their valuable contributions to the survey. None of them received additional compensation for this work.
Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or any other funding agencies.

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Trends in On-label and Off-label Modafinil Use in a Nationally Representative Sample

Modafinil is a nonamphetamine stimulant approved for narcolepsy, obstructive sleep apnea, and shift-work sleep disorder.[1] Off-label use is often recommended, but regulatory agencies have raised concerns about hypersensitivity reactions and neuropsychiatric adverse effects.[1,2] It is unclear how often and for which conditions modafinil is being prescribed in clinical practice.

Methods. Using the National Ambulatory Medical Care Survey, a nationally representative sample of ambulatory visits, we examined modafinil use from January 1, 2002, through December 31, 2009.[3] We categorized patients by whether or not they had an on-label indication for modafinil, defining *off-label use* as the absence of an on-label diagnosis, and examined the association between modafinil use and specific off-label indications.[1] We further examined modafinil use among patients treated by psychiatrists, neurologists, pulmonologists, and otolaryngologists relative to primary care physicians and other specialists. Finally, we examined the association between modafinil use and other centrally acting medications that might interact with modafinil: antidepressants, benzodiazepines, and amphetamines. In multivariate logistic regression, modafinil use was the outcome, and the predictor variables of interest were, in separate models, diagnostic indication, physician specialty, and concurrent medication. Analyses controlled for age, sex, race/ethnicity, payer, geographic region, and survey year. Analyses were survey weighted and performed using statistical software (Stata/IC, version 12; StataCorp). A supplemental description of our methods is available online (eMethods; http://www.jamainternalmed.com).

Results. The number of patients receiving modafinil increased almost 10-fold during the study period, from 57 768 in 2002 to 555 691 in 2009. On-label use increased by less than 3-fold, whereas off-label use increased more than 15-fold (**Figure**). Across all years, 89% of patients prescribed modafinil did not have an on-label diagnosis, and patients with depression and multiple sclerosis accounted for 18% and 12%, respectively, of all modafinil prescriptions. Multivariate analyses demonstrated an association between modafinil use and each examined potential off-label indication: multiple sclerosis, (odds ratio [OR], 84.6; 95% CI, 50.0-143.0), Parkinson disease (19.4; 6.7-56.1), chronic fatigue syndrome (23.4; 4.6-118.0), depression (10.8; 6.0-19.5), and attention-deficit/hyperactivity disorder (5.4; 2.3-12.6) relative to the absence of a given diagnosis (eTable 1). Patients

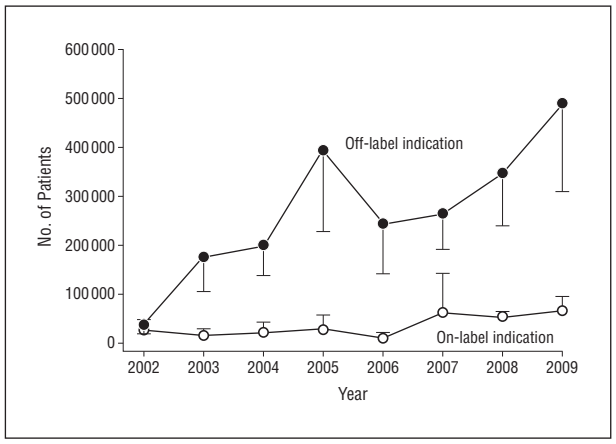

Figure. The number of patients receiving modafinil for on-label vs off-label use. Limit lines indicate standard error.

treated by psychiatrists (OR, 21.1; 95% CI, 13.2-33.7) and neurologists (19.7; 12.3-31.5) had higher odds of receiving modafinil relative to primary care physicians and other specialists, whereas patients seeing pulmonologists and otolaryngologists were not statistically more likely to be receiving modafinil (eTable 2). Each examined medication class was associated with increased odds of concurrently receiving modafinil: antidepressants (OR, 8.4; 95% CI, 5.4-13.2), benzodiazepines (5.0; 3.5-10.3), and amphetamines (8.7; 4.2-18.6). Altogether, 45% of patients receiving modafinil were also receiving an antidepressant, whereas 15% were receiving a benzodiazepine and 6%, an amphetamine.

Comment. These analyses indicate the rapid recent increase in modafinil use and suggest that most prescriptions are for off-label indications. That modafinil appears strongly associated with depression and multiple sclerosis is especially noteworthy given that the trials on which the US Food and Drug Administration approved modafinil excluded patients with such diseases.[4-7] Similarly, antidepressants and benzodiazepines were excluded from these trials.[4-7]

To place temporal trends into context, certain events related to modafinil's marketing and adverse event reporting should be noted. Cephalon, Inc, which markets modafinil, was sued by multiple US states for promoting modafinil for off-label indications and agreed to a multimillion dollar settlement in 2008.[8] This may suggest that some degree of off-label marketing was responsible for increases in off-label use. Nonetheless, substantial increases in modafinil use occurred between 2008 and 2009, after this case was settled. Of note, modafinil use declined substantially between 2005 and 2006. This may have been the result of reports released during that time of modafinil-associated hypersensitivity reactions.[9] Despite that precipitous 1-year decline, modafinil use soon recovered.

Our study has important limitations. Data about the specific diagnosis for which modafinil was prescribed were not available. In addition, only the top 3 diagnoses per encounter were listed, and we cannot exclude the possibility that an on-label indication may have existed. Nonetheless, the results strongly suggest that off-label indications are responsible for a large share of prescriptions given that patients receiving modafinil without an on-label diagnosis increased by 15-fold while those with an on-label diagnosis increased by only 3-fold. Also, off-label indications for which modafinil has commonly been recommended are strongly associated with its use. Finally, patients are much more likely to be receiving modafinil if they are being seen by a psychiatrist or neurologist—specialists who treat off-label indications, such as depression, multiple sclerosis, and Parkinson disease.

Modafinil use is increasing rapidly, which appears in large part to result from off-label prescribing. Given that modafinil is often being used in patients with comorbid conditions and concurrent medications that do not reflect the populations that formed the basis for regulatory approval, this raises concerns about the potential for adverse events and indicates the need for further study of unapproved indications.

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Published Online: March 18, 2013. doi:10.1001/jamainternmed.2013.2807
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Conflict of Interest Disclosure: None reported.
Funding/Support: This research was supported by grant K23 HL102159 from the National Heart, Lung, and Blood Institute, National Institutes of Health.
Online-Only Material: The eMethods and eTables are available at http://www.jamainternalmed.com.

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Tuning Fork Testing in Sudden Sensorineural Hearing Loss

Sudden sensorineural hearing loss (SNHL) is a condition for which prompt diagnosis and initiation of treatment is of paramount importance.[1] Because patients frequently seek initial evaluation in urgent care or primary care settings, audiologic assessment may not be immediately available. As such, tuning forks have the potential to assist with initial treatment and appropriate triage because they are available, inexpensive, and easy to use. However, the role of tuning fork testing in the initial workup of hearing complaints has not been clearly elucidated.[2,3]

A recent multicenter, randomized controlled clinical trial compared oral and intratympanic corticosteroids for sudden SNHL.[4] Tuning fork testing and formal audiometry were performed as part of the baseline assessment of eligible study participants, creating a robust database that facilitates a prospective evaluation of the utility of the Weber test in this setting. We hypothesized that the Weber test would be a useful clinical metric to diagnose unilateral SNHL.

Methods. *Study Design*. This study uses data that determined whether patients were eligible to participate in a prospective multicenter, randomized, clinical trial that compared different treatments for sudden unilateral SNHL (clinicaltrials.gov NCT00097448).[4] The trial was conducted from 2004 through 2009 and was approved by the institutional review boards of all participating sites.

Participant Recruitment. Adult patients who presented with unilateral idiopathic sudden SNHL were included. Audiometric criteria for inclusion were a documented pure tone average (PTA) of at least 50 dB in the affected ear, and at least a 30-dB difference between ears in at least 1 of the 4 PTA frequencies.

Hearing Evaluation. The Weber test was administered with a 512-Hz tuning fork at screening or enrollment. To perform the Weber test, 1 tine of the tuning fork was struck forcefully enough for the examiner to perceive sound. The fork was placed firmly on the scalp vertex, forehead, or maxillary dentition. The patient reported whether sound was perceived better in either ear or heard in the midline.[5] Audiometric evaluation was performed thereafter; variables for each ear included frequency thresholds and PTA.

Statistical Analysis. The results of the Weber test at the time of study enrollment were compared with the results of the audiogram. The sensitivity of the Weber test was calculated. κ Coefficients were calculated to quantify the magnitude of agreement between the Weber test and the PTA. McNemar test was used to test whether the identification of the affected ear by the Weber test was concordant with the PTA results. These analyses were performed for the entire data set (n=250), as well as for the subset of patients for whom the Weber test lateralized (n=198).

Results. The Weber test correctly lateralized to the ear opposite the hearing loss in 196 of patients (78%). Of the remaining 22%, 2 cases (1%) incorrectly lateralized, falsely indicating conductive loss; 38 (15%) were heard in the midline, and 14 (6%) were not heard. Despite good overall agreement between the audiogram results and the Weber test with low discordance, the Weber test did not reliably predict the audiogram results for the entire cohort. Among the subset of patients for whom the Weber test lateralized (n=198), the Weber test correlated considerably better, and was a reliable predictor of the audiogram results (**Table**).

Table. Comparison of Weber Test to Audiogram in Sudden Sensorineural Hearing Loss

Parameter	All Patients (n = 250)	Subset for Whom Weber Test Lateralized (n = 198)
Sensitivity, %	78	99
Overall agreement[a]	0.82	0.98
P value[b]	.19	.50
AUC[b]		
500 Hz	0.56	0.80
P value	.09	<.001
PTA[b]	0.56	0.88
P value	.09	<.001

Abbreviations: AUC, area under curve; PTA, pure tone average (the arithmetic mean of the hearing thresholds at 500, 1000, 2000, and 4000 Hz).
[a] κ Coefficient.
[b] *P* value calculated by McNemar test.

Comment. Since most patients who experience a sudden SNHL are seen in a primary care setting, and since more common conditions are often difficult to distinguish based on clinical assessment alone, referral for specialty evaluation and audiometry are frequently delayed beyond the ideal therapeutic window.[6] This study was undertaken to evaluate whether the Weber test might help identify patients with suspected SNHL who require prompt referral and treatment. The finding that the Weber test did not lateralize or could not be heard in over 20% of study participants was consistent with other reports that conclude that Weber test results can be unreliable.[2,3]

The high reliability of the Weber test when it lateralized away from the suspect ear confirms that the test retains value in the clinical setting when assessing a patient presenting with acute hearing complaints. Most patients with alternative diagnoses routinely considered by primary care providers, such as cerumen impaction, Eustachian tube dysfunction, or otitis media, will present with a conductive hearing loss. Thus, if a Weber