Supplementary Online Content


eMethods. Supplemental methods

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eTable 1. Diagnoses associated with receiving modafinil

eTable 2. Physician specialty associated with receiving modafinil

This supplementary material has been provided by the authors to give readers additional information about their work.
Data Source

We analyzed data from the National Ambulatory Medical Care Survey (NAMCS) from 2002 to 2009, the last year of available data at the time of analyses. NAMCS is an annual survey conducted by the National Center for Health Statistics (NCHS) which collects data on ambulatory medical utilization in the U.S.\textsuperscript{1-4} A multistage probability design is applied in order to collect a nationally representative sample of patient visits to office-based and community health center-based physicians.\textsuperscript{1} The first stage is a probability sample of geographically defined primary sampling units (PSU), the second stage samples practicing physicians within each PSU, and the third stage samples patient visits within a given practice. Characteristics of the sampled patient visit are documented using a survey tool.\textsuperscript{1,2} All data are weighted to produce nationally representative estimates.\textsuperscript{1,2} As recommended by the NCHS, we adjusted for the frequency of patient visits, and as a result, patient visit estimates mirror the actual distribution of patient visits in the United States.\textsuperscript{5} Modafinil is not approved by the FDA for use in children, and we limited our analyses to patients over 18 years of age.\textsuperscript{5} This study was exempt from review by the Institutional Review Board because NAMCS is publicly available and uses no patient identifiers.
Measures

Diagnostic Classifications

NAMCS collects up to three diagnoses per patient visit based on the International Classification of Diseases, Ninth Revision (ICD-9) coding system.\(^7\) We categorized patients as either having or not having an FDA-approved (on-label) indication for modafinil among their listed diagnoses. We defined off-label usage as the lack of an on-label diagnosis. FDA-approved indications for receiving modafinil were defined as: [1] narcolepsy (ICD-9 codes 347.0x and 347.1x: narcolepsy with and without cataplexy), [2] shift-work sleep disorder (327.36: circadian rhythm sleep disorder, shift work type, 307.45: circadian rhythm sleep disorder of nonorganic origin, and 780.55: disruptions of 24 hour sleep wake cycle, unspecified), and [3] obstructive sleep apnea (OSA). The definition of OSA included all ICD-9 codes for sleep apnea (327.20, 327.23, 327.29, 780.51, 780.53 and 780.57) except those specific to central sleep apnea (327.21 and 327.27); we chose this approach because sleep apnea is often coded generically, without specifying whether it is obstructive or central in origin, and obstructive sleep apnea is far more common than central sleep apnea.\(^8\)

We also examined specific potential off-label indications for modafinil, selected a priori based on previous research suggesting efficacy of modafinil for indications currently not FDA-approved.\(^9\) These diagnosis were defined, based on ICD-9 codes, as: [1] attention deficit hyperactivity disorder (ADHD) (ICD-9: 314.x), [2] chronic fatigue syndrome (780.71), [3] depression (major depression, single episode 296.2x, major depression, recurrent episode 296.3x, and depressive disorder not otherwise specified 311.00), [4] bipolar disorder (single manic episode 296.0x, recurrent episodes 296.1x, current manic or depressive episode 296.4x-296.7x, bipolar non-specified episode 296.8x), [5] multiple sclerosis (340.x) and [6] Parkinson’s disease (332.x).\(^7\)

Because up to three diagnoses may be present, the possibility of more than one diagnostic indication existed. Mutually exclusive indications for modafinil were assigned using
the following criteria: (1) patients with any on-label diagnosis for modafinil were assigned to that
diagnostic indication in preference to any off-label diagnoses that might be present and (2) for
patients who had more than one on-label or off-label indication listed, the diagnosis listed first in
the hierarchy was chosen as the indication. For example, if multiple sclerosis was listed as the
primary diagnosis and depression as a secondary diagnosis, the indication for modafinil was
categorized as multiple sclerosis.

Physician Specialty

Our intent here was to investigate the relative likelihood of various physician specialties
prescribing modafinil. We therefore specifically examined those specialties most likely to
prescribe modafinil, for either the on- or off-label indications discussed above. We thus
categorized physicians a priori as: psychiatry, neurology, pulmonary/critical care,
otolaryngology, or other (which included primary care and other specialties), the last category
being the referent group for analyses.

Medication Ascertainment

The NAMCS survey records medications being taken by a patient at the time of any
given visit, and we used these records to classify whether or not patients had been prescribed
modafinil. Additionally, to gain insight into potential medications interactions, we investigated
the likelihood of three specific classes of medications being prescribed concurrently alongside
modafinil: antidepressants, benzodiazepines, and amphetamines. We coded medications using
the Lexicon drug database coding system, and medications were classified as antidepressants
if they were approved by the Food and Drug Administration (FDA) for the treatment of major
depressive disorder.1,17

We chose these three medication classes because, like modafinil, they act on the central
nervous system (CNS) and because, like modafinil, they are often recommended for mood or
Patients using these medications were also excluded from the trials of modafinil on which FDA approval was based.23-28

Statistical Analyses

Statistical analyses were performed using Stata/IC version 12 (College Station, TX). The NAMCS provided the patient visit weights, strata and primary sampling unit design variables which we used for the analyses.¹

To establish the extent of use and trends in on- versus off-label use of modafinil, we examined the number of patients prescribed modafinil over the study period, categorizing patients by whether or not they had an on-label indication for modafinil. We also examined trends over time in modafinil usage associated with the aforementioned pre-specified on- and off-label indications.

We also developed multivariate logistical regression models to determine independent associations between modafinil usage and both physician specialty and diagnostic indications. In these analyses, modafinil usage was the outcome and the predictor variables of interest were, in separate analyses, physician specialty or diagnostic indication. We controlled for sociodemographic factors and survey year in these multivariable analyses. The specific sociodemographic characteristics that we controlled for were: age, gender, race/ethnicity (categorized as non-Hispanic White, Black, Hispanic, and Other Race), geographic region (Northeast, Midwest, South, and West), insurance type (commercial, Medicare, Medicaid, uninsured, and other (including worker's compensation and unknown). To reduce bias from missing data for race/ethnicity, we used imputed data produced by the NHCS.¹

Finally, we examined the strength of the associations between modafinil usage and usage of three different medication classes: antidepressants, benzodiazepines and amphetamines. We applied logistic regression with modafinil usage (yes vs no) as the outcome and, separately, each medication class as the predictor of interest, controlling for
sociodemographic factors and survey year in each of the three multivariable logistic regressions.
eReferences


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eTable 1. Diagnoses associated with receiving modafinil

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>% With Diagnosis*</th>
<th>Odds Ratio† (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On-label indications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>6.7%</td>
<td>666 (268-1655)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>4.7%</td>
<td>6.8 (3.5-13.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shift-Work Sleep Disorder</td>
<td>0.001%</td>
<td>11.8 (0.86-162)</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Off-label indications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>2%</td>
<td>5.4 (2.3-12.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome</td>
<td>0.01%</td>
<td>23.4 (4.6-118)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression</td>
<td>18.4%</td>
<td>10.8 (6.0-19.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>4.1%</td>
<td>9.4 (5.0-17.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>12.2%</td>
<td>84.6 (50.0-143)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>2.5%</td>
<td>19.4 (6.7-56.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*The percentage of patients using modafinil who had the listed diagnosis (e.g. 6.7% of patients using modafinil were diagnosed with Narcolepsy).

† Odds of receiving modafinil when the listed diagnosis was present relative to when this diagnosis was absent, from separate logistic regression analyses in which modafinil usage was the outcome and the listed diagnosis was the predictor of interest in a multivariable model controlling for: age, gender, race/ethnicity, insurance type, geographic region, and survey year. Thus, each odds ratio in this table presents results from a distinct model.
**eTable 2.** Physician specialty associated with receiving modafinil*

<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care &amp; Other Specialties</td>
<td>1.0 [Reference]</td>
<td>N/A</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>21.1 (13.2-33.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neurology</td>
<td>19.7 (12.3-31.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulmonary &amp; Critical Care</td>
<td>2.7 (0.3-21.9)</td>
<td>.35</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>0.7 (0.2-2.7)</td>
<td>.84</td>
</tr>
</tbody>
</table>

* Results are from a single logistic regression analysis in which modafinil usage was the outcome variable and physician specialty was the multi-level predictor variable of interest in a multivariable model controlling for: age, gender, race/ethnicity, insurance type, geographic region, and survey year. Thus, this entire table presents results from one model.