ORIGINAL ARTICLE

Retrospective Review of Trend in Modafinil Overexposures Reported to American Poison Information Centers

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Abstract

Background: Modafinil, a non-amphetamine central nervous system stimulant, is a wakefulness-promoting agent indicated for use in shift work sleep disorder, narcolepsy, and obstructive sleep apnea. The trend in modafinil overexposure over a ten-year period and the population likely to experience a resulting clinical effect is evaluated.
Methods: Using data from the American Association of Poison Control Center (AAPCC) National Poison Data System (NPDS), a retrospective review of all reported modafinil overexposures over a ten-year period (2001-2010) was conducted. In order to determine whether age, reason and acuity had a role in predicting medical outcome, odds ratios (OR) were calculated using binomial logistic regression analysis.
Results: There were 1,100 modafinil overexposures reported with known outcomes, of which 600 cases (54%) were women and 367 (33%) were ≤ 5 years old. Seventy-seven percent of the exposures were acute ingestions and the majority was unintentional. The number of reported modafinil exposures increased with time until 2007. Adults were more likely to have an adverse effect than children ≤ 5 years of age. Patients with an intentional overexposure were more likely to have an effect than those with an unintentional overexposure (OR = 5.2; 95% CI 3.9-7.1; P < 0.001).
Conclusion: The frequency of reported modafinil exposures increased with time until 2007. The majority of exposures resulted in no adverse clinical effect. Older patients and those with intentional exposure were more likely to experience a clinical effect.

Keywords: Central Nervous System Stimulants; Drug Overdose; Modafinil; Poison Control Centers; United States

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INTRODUCTION

Modafinil (2[(diphenylmethyl) sulfinyl] acetamide) is a non-amphetamine central nervous system stimulant that is used as a wakefulness-promoting agent (1-3). Approved by the Federal Drug Administration (FDA) in 1998 under the brand name Provigil®, it is indicated for the treatment of drowsiness associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder (2,3). Due to its presumed lower potential for abuse and lack of peripheral sympathomimetic effects that are associated with the amphetamine stimulants, it has also been studied and used off-label to treat sedation in other conditions such as Parkinsonism, fatigue in human immunodeficiency virus (HIV) infection, multiple sclerosis, cancer, and attention deficit hyperactivity disorder (ADHD) (4-8). Other off-label uses include the treatment of cocaine dependence and withdrawal, alcoholic organic brain disorder, and as adjunct therapy in depression (2,3,9,10).

The mechanism of action of modafinil is complex and poorly understood. It is known to cause a decrease in γ- aminobutyric (GABA) release and increase glutamate release in the hippocampus and thalamus (11). Additionally, it is known to increase extracellular concentrations of dopamine, norepinephrine, serotonin, glutamate, and histamine (11). However, unlike the amphetamines, modafinil does not have an effect on spontaneous dopamine release. The standard therapeutic dose of modafinil in adult patients is 200-400 mg daily.

A search of the medical literature revealed limited information regarding supratherapeutic modafinil ingestions. During clinical trials, ingestions of doses up to 4,500 mg were reported without any life-threatening toxicity (1). Clinical effects of these supratherapeutic ingestions were evaluated in two studies and 2 case reports (2,3,12,13). Available information suggests that the most common clinical effects include tachycardia, insomnia, agitation and headache (2,3). The majority of ingestions, however, resulted in either minor severity or an absence of effects (2,3). Both Spiller et al. and Carstairs et al. found that the majority of ingestions reported to a limited number of American poison control centers involved patients less than 6 years of age (2,3). No deaths associated with modafinil

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overdose alone have been reported (1).

Due to the off-label use for cognitive enhancement in psychiatric disorders such as schizophrenia and ADHD, modafinil and other stimulant medications have been sought by healthy individuals in order to improve cognitive function (14-16). Modafinil has been shown to improve neuropsychological performance, improve short term memory, and boost the individual's ability to plan and process information when used at doses of 100 or 200 mg in healthy individuals (14,15,17). In a poll of 1,400 individuals conducted by the University of Cambridge, 1 in 5 respondents reported that they had taken cognitive enhancing medications for non-medical purposes to improve their focus and concentration (17). Of those who confirmed using cognitive enhancing medications, 44% reported using modafinil.

To our knowledge, no study to date has investigated the 10-year trend in modafinil exposures reported to poison control centers in the United States. Therefore, we performed a retrospective review of modafinil overexposure as reported to American poison information centers in order to determine whether an increased incidence of modafinil exposures was observed. Secondarily, we sought to determine which populations were most likely to experience a resulting adverse clinical effect.

METHODS

A retrospective review of all cases of modafinil exposure reported to the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) was conducted. Cases are voluntarily reported to American poison information centers via a national telephone number and can involve adverse reactions, unintentional or intentional ingestions, or bites/envenomations. Data were reported to the AAPCC by poison information centers within the United States. One of the authors (EPK) was awarded a data grant by the AAPCC for those data reported to the AAPCC from 2001 to 2010. Prior to analysis, these data were extracted from a Microsoft® Access database and converted to a Microsoft® Excel database. Modafinil exposures were identified using unique seven-digit product codes for modafinil and Provigil. Inclusion criteria were single substance exposure to modafinil and follow-up to a known outcome. Exclusion criteria were cases with history of coingestion of other medications and the inability to follow patients to a known outcome.

Table 1. Pertinent National Poison Data System (NPDS) coding field definitions

Field	Definition
Acuity of exposure	
Acute	Exposure that occurred over a period less than or equal to 8 hours.
Acute-on-chronic	A single ingestion that was preceded by an exposure occurring over a period exceeding 8 hours.
Chronic	Exposure to the same substance over a period exceeding 8 hours.
Reason for exposure	
Unintentional – general	Exposure that does not meet the description as detailed below.
Unintentional – environmental	Passive exposures that do not occur in the workplace involving contamination of air, soil, or water.
Unintentional – occupational	Exposure that occur as a direct result of the patient being in the workplace or on the job.
Unintentional – therapeutic error	Inadvertent deviations from proper therapeutic dosing instructions.
Unintentional – misuse	Exposure that is not planned and is unforeseen involving the wrongful use of a non-pharmaceutical substance.
Unintentional – bite/sting	All animal bites and stings, regardless of whether or not the patient is envenomated.
Unintentional – food poisoning	Suspected or confirmed food poisoning.
Unintentional – unknown	Exact reason of the unintentional ingestion is unknown.
Intentional – suspected suicide	Substance is ingested in a self-harm attempt.
Intentional – misuse	Improper use of a substance for reasons other than psychotropic effects.
Intentional – abuse	Improper use of a substance in an attempt to gain a high, euphoric or psychotropic effect.
Intentional – unknown	Exact motive for intentional ingestion is unknown.
Adverse reaction – drug	Undesired symptoms secondary to an allergic, hypersensitivity, or idiopathic response to the active ingredients, inactive ingredients, or excipients of a substance.
Medical outcome	
No effect	No symptoms develop as a result of the exposure.
Minor effect	Some symptoms develop as a result of the exposure but they are minimally bothersome to the patient.
Moderate effect	The patient exhibits symptoms as a result of the exposure that are not life-threatening and no residual disability or disfigurement results.
Major effect	Patient develops life-threatening symptoms or significant residual disability/disfigurement as a result of the exposure.
Death	Patient died as a result of the exposure.

All personal identifiers were cleansed from the data prior to its receipt by investigators. Data collected included date of reported exposure, age, gender, reason for exposure, acuity of exposure and clinical outcome. Standard definitions for acuity of exposure, reason for exposure and medical outcomes were used by all US poison centers, the details of which are highlighted in Table 1 (18). Clinical manifestations of reported cases were not collected as the clinical effects of modafinil overdose have been previously described (2,3,12,13).

Statistical analysis was performed using SPSS version 19 (IBM Corp., Armonk, NY, USA). Odds ratios obtained from binomial logistic regression were used to estimate the risk of experiencing a clinical effect from modafinil ingestion according to age, acuity of exposure, and reason for exposure. Individual outcomes including "minor effect", "moderate effect" and "major effect" were combined for the multivariate logistic regression. Unadjusted odds ratios were calculated to determine whether a variable (age, reason, or acuity) had an effect on outcome. Adjusted odds ratios were calculated to determine whether a variable (age, reason, or acuity) has an effect on clinical outcome when the other two variables were held constant. This study was determined to be exempt by the University of Pittsburgh Institutional Review Board.

RESULTS

A total of 2,154 cases of modafinil ingestion were reported to the NPDS between 2001 and 2010. The trend in reported exposures is illustrated in Figure 1. As it is shown, the frequency of reported modafinil exposures has not continued to rise over time. A notable rise occurred prior to 2008, with a peak of 162 cases reported in 2007. Thereafter, exposures declined toward levels observed during the first three years of the study period.

After excluding cases that were confirmed non-exposures and those that lacked follow-up to a known outcome, 1,100 cases were enrolled in the study. Table 2 shows the patient characteristics for reported overexposures according to medical outcome. Of all reported modafinil ingestions, 600 cases (54%) involved female patients. Three hundred sixty-seven patients (35%) were less than or equal to 5 years of age and 244 (23%) were between 30 and 49 years of age. No clinical effect was observed in 532 cases (48%). Three hundred two exposures (27%) were intentional. Of the intentional exposures, 203 cases (67%) were suspected suicide attempts and 47 (16%) were reported abuse. Table 3 shows the reason for ingestion according to age. Abuse was reported most frequently in the 18-29 and 30-49 year-old age groups with 17 exposures reported in each group.

Results of the binomial logistic regression can be seen in Table 4. Patients 18-29 years of age were 4.6 times more likely to experience an adverse clinical effect as a result of modafinil ingestion as compared to patients 0-5 years of age (OR = 4.6; 95% CI 2.7-7.7; P < 0.001). Compared to patients 5 years old or younger, all other age groups were more likely to experience a clinical effect. Results remained significant after controlling for reason and acuity. Compared to unintentional exposures, all other exposure types were more likely to experience an adverse clinical effect; after controlling for age and acuity, the results remained significant. Acute-

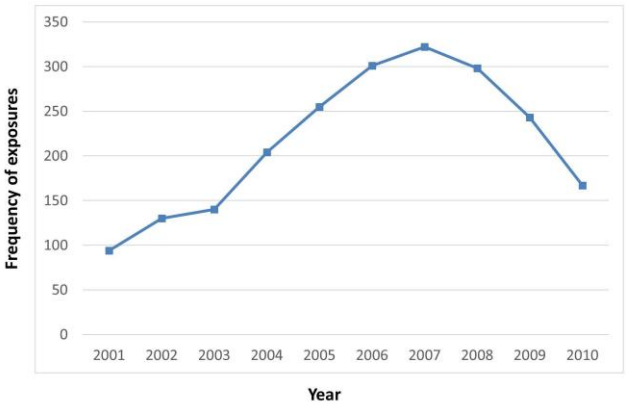

Figure 1. Frequency of reported modafinil exposures from January 1st 2001 through December 31th 2010, by year (n = 2154)

Table 2. Characteristics of reported modafinil overexposures by medical outcome

		Age (years)					Gender		Acuity			Reason					
	n	≤5	6-17	18-29	30-49	>50	Male	Female	Acute	Acute-on- Chronic	Chronic	Abuse	Misuse	Suspected Suicide	Unintentional	Adverse Reaction	Other/ Unknown
No effect	532	286	65	42	73	55	276	256	451	74	3	10	8	57	453	1	1
Effect	568	81	67	124	171	95	223	344	385	143	26	37	44	146	262	69	10
Minor	339	60	36	67	93	61	137	202	234	83	18	20	25	66	185	38	5
Moderate	222	21	31	55	74	33	82	139	146	58	8	17	18	76	75	31	5
Major	7	0	0	2	4	1	4	3	5	2	0	0	1	4	2	0	0
Total	1100	367	132	166	244	150	499	600	836	217	29	47	52	203	715	79	13

on-chronic exposures were more likely to experience a clinical effect (OR = 2.3; 95% CI 1.7-3.1; P < 0.001) than acute exposures. After controlling for age and reason, this likelihood was no longer significant.

DISCUSSION

Optimization of cognitive performance is purportedly popular at colleges and universities in the United States. Students and professors have reported using cognitive enhancement drugs in order to improve their performance and productivity (19). Extending beyond the collegiate setting, the US military has investigated the use of pharmaceutical agents, such as modafinil, to improve neuropsychological function (17,19). Modafinil has been investigated as a potential aid in enhancing cognitive function in healthy adults (14,15). With the desire to outperform colleagues, one might expect a rising trend in the use and abuse of medications like modafinil. However, our study evaluated the trend in modafinil ingestion over a ten-year period and found only 4% of all reported exposures to be due to abuse.

A peak in modafinil ingestions was observed prior to 2008. Certain events related to the marketing of modafinil are important to note. The producer of modafinil, Cephalon Inc., was sued by multiple US states for promoting the off-label use of modafinil (20). As a result, in 2008, a multi-million dollar settlement was made. In our study, a notable decrease in reported ingestions occurred beginning in 2008. Penaloza et al. found that 89% of all patients prescribed modafinil are taking the medication for off-label uses, with depression and multiple sclerosis accounting for the largest portion of these off-label indications (20). Given that the majority of patients prescribed modafinil were taking the medication for an off-label indication, the drop in exposures reported may potentially be explained by the settlement in 2008. Furthermore, a fictitious press release was allegedly disseminated in 2008 that reported that the National Institute of Health was "cracking down on scientists' brain doping" (21). This press release purportedly linked readers to a webpage for the World Anti-Brain Doping Authority, which was likewise fabricated (21). This spurious press release may have caused a decline in the use modafinil for this purpose. Lastly, the total number of human exposure calls reported to American poison information centers, however, also declined beginning in 2008 through 2010, which may also explain the decrease in exposure calls involving modafinil (22).

Reported ingestions in college-aged individuals and those in the age range of 18-29 years, only accounted for 16% of all reported modafinil exposures over the study period.

Table 3. Reason for reported modafinil overexposures by age

Reason	Age (years)				
	≤5	6-17	18-29	30-49	>50
Intentional					
Abuse	0	9	17	17	1
Misuse	0	3	19	18	7
Suspected suicide	0	35	68	72	20
Unintentional	366	79	41	111	103
Adverse Reaction	1	5	17	22	17
Other	0	1	4	4	2
Total	367	132	166	244	150

Table 4. Risk of experiencing a clinical effect according to age, reason and acuity of exposure

Risk Factor	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (years)				
≤5	----	----	----	----
6-17	3.6 (2.3-5.4)	< 0.001	2.3 (1.4-3.6)	0.001
18-29	10.4 (6.8-16.0)	< 0.001	4.6 (2.7-7.7)	< 0.001
30-49	8.3 (5.7-12.0)	< 0.001	4.5 (2.9-6.9)	< 0.001
≥50	6.1 (4.0-9.2)	< 0.001	4.0 (2.5-6.4)	< 0.001
Reason				
Unintentional	----	----	----	----
Intentional	5.2 (3.9-7.1)	< 0.001	2.8 (1.9-4.0)	< 0.001
ADR	119 (16-864)	< 0.001	51 (7-375)	< 0.001
Acuity				
Acute	----	----	----	----
Acute-on-chronic	2.3 (1.7-3.1)	< 0.001	1.0 (0.7-1.5)	0.88
Chronic	10.2 (3.0-33.8)	< 0.001	2.3 (0.6-8.4)	0.21

OR: Odds ratio; CI: Confidence interval; ADR: Adverse drug reactions

Furthermore, abuse was reported at the same frequency in the 18-29 and 30-49 year-old age group. Despite reports propagated by the media, it does not appear that the 18-29 year-old age group accounts for modafinil exposures at rates markedly higher than other age groups. Although the reason for ingestion could not be further classified beyond "misuse" and "abuse," the small portion of ingestions by this age group may suggest that modafinil use for cognitive enhancement may not be as big of a problem as perceived by the media. Given the lower potential for abuse and the small number of FDA approved indications for modafinil, patients may be less apt to seek this medication individually for recreational purposes.

LIMITATIONS

Our study was limited by the fact that the frequency of modafinil ingestions was directly dependent on the exposure being reported voluntarily to one of the 57 poison control centers in the US and the inherent limitations of AAPCC NPDS data. Furthermore, we were unable to obtain national prescription rates over the ten-year period. Had we been able to normalize the number of reported exposures according to the number of prescriptions written per year, a more accurate representation of exposures accounting for a potential decrease in access to modafinil may have been possible.

The presence of coingestants was excluded from our study in order to provide a more accurate portrayal of the clinical effects of supratherapeutic modafinil ingestions, which may have decreased the number of cases included in this study.

CONCLUSION

A continual increase in modafinil exposure over the ten-year period was not observed. After 2007, the frequency of reported exposures decreased toward the frequency of ingestions reported during the first three years of the study period. The majority of reported exposures involved females, and children aged less than or equal to 5 years of age. Acute, unintentional exposures were most common and modafinil overexposures usually resulted in no clinical effect. Compared to patients less than or equal to 5 years of age, all other age groups were more likely to experience a clinical effect. Intentional exposures were more likely to experience a clinical effect.

Declaration of interest: The American Association of Poison Control Centers (AAPCC; http://www.aapcc.org/) maintains the national database of information logged by the country's poison control centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s). The authors report no other declarations of interest.

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