Pregnancy and Fetal Outcomes Following Exposure to Modafinil and Armodafinil During Pregnancy

Although results of animal studies have shown reproductive toxic effects with use of modafinil and armodafinil, data on exposure during pregnancy in humans are limited.[1,2] The US Provigil/Nuvigil Pregnancy Registry, a postmarketing requirement with data annually reported to the US Food and Drug Administration, was established to evaluate pregnancy and fetal outcomes in individuals who could become pregnant and received these drugs during pregnancy. This report provides results from cumulative data as of February 2019.

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Methods | The US Provigil/Nuvigil Pregnancy Registry is part of an ongoing, prospective cohort study established in February 2010. Enrollment in the registry is open on a voluntary basis to any individual exposed to modafinil and/or armodafinil within 6 weeks prior to conception or during pregnancy. Those wishing to participate are required to provide informed consent and the contact information of their clinician, and must agree to be contacted periodically. The registry is posted on relevant websites, including FDA.gov and ClinicalTrials.gov, as well as on product labeling, which specifies a toll-free telephone number to the registry. Outreach efforts for patient recruitment included direct mail to health care professionals. This study was approved by Advarra Institutional Review Board.

A pregnancy was classified as prospective if enrollment occurred before knowledge of the pregnancy outcome or detection of a congenital malformation at a prenatal test. A pregnancy was classified as retrospective if enrollment occurred after knowledge of the pregnancy outcome or congenital malformation at a prenatal test.

Pregnancy and fetal outcomes were adjudicated by an independent registry advisory committee. The primary end point was major congenital malformations (MCMs) using the Metropolitan Atlanta Congenital Defects Program classification. Additional pregnancy outcomes included spontaneous abortion (<20 weeks' gestation), elective pregnancy termination, and fetal death (≥20 weeks' gestation).

Results | From February 2010 to February 2019, 148 individuals were enrolled in the registry; 81 received modafinil during pregnancy, 66 received armodafinil, and 1 received both modafinil and armodafinil (**Table 1**). Narcolepsy was the main indication reported (102 of 145 [70%]).

Of the 122 prospective pregnancies, 110 had known outcomes at cutoff date (**Table 2**). Among 102 prospective live births, 13% (n = 13) had MCMs, which is above the prevalence of about 3% in the general population.[3] Of these live births with MCMs, 4 had congenital torticollis, 2 had hypospadias, and 3 had congenital heart defects, of which the latter yielded a cardiac malformation prevalence of 3% compared with about 1% in the general population.[4] The prevalence of MCMs in the 97 prospective live births exposed during the first trimester was 13% (n = 13). Pooling the data for both prospective and retrospective live births resulted in the same MCM prevalence of 13% observed in prospective live births alone.

Discussion | Results of this analysis demonstrate that there is a potential increased risk of MCMs following in utero exposure

Table 1. Demographic and Baseline Characteristics for Pregnant Individuals Exposed to Modafinil and Armodafinil, 2010-2019

Demographic variables	No. (%)[a]		
	Prospective (n = 122)	Retrospective (n = 26)	Total (N = 148)
Exposure[b]			
Total No.	122	26	148
Modafinil	62 (51)	19 (73)	81 (55)
Armodafinil	59 (48)	7 (27)	66 (45)
Modafinil and armodafinil	1 (1)	0	1 (1)
Pregnant individual age			
Total No.	122	26	148
Median (range), y	31 (20-40)	31 (21-35)	31 (20-40)
Race			
Total No.	104	20	124
White	95 (91)	20 (100)	115 (93)
Other[c]	9 (9)	0	9 (7)
Education			
Total No.	105	20	125
High school graduate or higher	66 (63)	11 (55)	77 (62)
Prepregnancy BMI			
Total No.	97	15	112
Mean (SD)	27 (6)	26 (7)	27 (6)
Trimester of exposure			
Total No.	118	25	143
First trimester	115 (97)	22 (88)	137 (96) 1 (1)

(continued)

Table 1. Demographic and Baseline Characteristics for Pregnant Individuals Exposed to Modafinil and Armodafinil, 2010-2019 (continued)

Demographic variables	No. (%)[a]		
	Prospective (n = 122)	Retrospective (n = 26)	Total (N = 148)
Comorbidities[d]			
Total No.	120	25	145
Narcolepsy	85 (71)	17 (68)	102 (70)
Depression	39 (33)	4 (16)	43 (30)
Preeclampsia or pregnancy-induced hypertension	15 (13)	4 (16)	19 (13)
Diabetes	5 (4)	1 (4)	6 (4)
Gestational diabetes	5 (4)	0	5 (3)
Concomitant medications[d]			
Total No.	120	25	145
Prenatal vitamins	89 (74)	16 (64)	105 (72)
Selective serotonin reuptake inhibitors	33 (28)	1 (4)	34 (23)
Antihistamines	21 (18)	4 (16)	25 (17)
Thyroid hormones	20 (17)	4 (16)	24 (17)
5-HT_3 and other antiemetics[e]	16 (13)	5 (20)	21 (14)
Folic acid	13 (11)	3 (12)	16 (11)
Antidepressants	12 (10)	3 (12)	15 (10)
Antiepileptic	11 (9)	1 (4)	12 (8)
Benzodiazepines	10 (8)	0	10 (7)
Proton-pump inhibitors	8 (7)	3 (12)	11 (8)
Use during pregnancy			
Tobacco			
Total No.	111	20	131
Yes	11 (10)	1 (5)	12 (9)
Alcohol			
Total No.	111	20	131
Yes	4 (4)	1 (5)	5 (4)
Illicit drug			
Total No.	111	20	131
Yes	0	1 (5)	1 (1)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Percentages are calculated using total number reported in each category as the denominator.

[b] Percentage may not add up to 100% because of rounding.

[c] Including Black individuals, Asian individuals, and individuals of unknown race/ethnicity.

[d] Patients can be counted in multiple groups, so percentages do not add to 100%.

[e] Including serotonin 5-HT_3 receptor antagonists (eg, ondansetron).

Table 2. Pregnancy Exposure to Modafinil and Armodafinil, 2010-2019

Characteristic	No. (%)		
	Prospective	Retrospective	Total
Pregnancies (by individual)			
Total No.	122	26	148
Lost to follow-up	4 (3)	0	4 (3)
Pregnancies complete (known outcomes)	110 (90)	26 (100)	136 (92)
Outcome pending	8 (7)	0	8 (5)
Pregnancies with known outcomes (by fetus)[a]			
Total No.	116	26	142
Live birth	102 (88)	17 (65)	119 (84)
Major congenital malformations[b]	13 (13)	3 (18)	16 (13)
Spontaneous abortion	13 (11)	8 (31)	21 (15)
Elective termination[c]	1 (1)	1 (4)	2 (1)
Fetal death	0	0	0

[a] Including 6 twin fetuses.

[b] Percentage is calculated of total live births.

[c] Termination in prospective case was because of diagnosis of trisomy 21 and in retrospective case because of unknown reasons.

to modafinil and/or armodafinil compared with the general population. This potential risk is not likely due to the underlying condition of narcolepsy, because previous data suggest that narcolepsy does not increase the risk of abnormal pregnancy outcomes.[5,6] Moreover, an analysis of first-trimester exposure confirmed the higher potential risk for MCMs. These findings are consistent with a previously published Danish retrospective database study reporting an absolute risk of 12% for MCMs in first-trimester pregnancy exposure to modafinil.[2] Because no specific organ malformation pattern was identified, a clear causal association between use of modafinil and/or armodafinil and MCMs cannot be established.

The limitations of this study include selection bias owing to voluntary enrollment, information bias owing to incorrect or incomplete data reporting, lack of internal comparison group, and a small sample size.

Although the available data are inconclusive for causality, the potential increased risk of MCMs provides an impetus for health care professionals to enhance the benefit-risk monitoring of modafinil and/or armodafinil use in pregnant individuals and individuals who may become pregnant.

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Invited Commentary

Caution in Prescribing Modafinil and Armodafinil to Individuals Who Could Become Pregnant

In their Research Letter, Kaplan and colleagues[1] report the teratogenicity of modafinil and/or armodafinil used within 6 weeks of becoming pregnant and during pregnancy based on data from the US Provigil/Nuvigil Pregnancy Registry. Of 102 prospective live births, 13% (n = 13) had major congenital malformations, a prevalence higher than the approximately 3% in the general population. Among these newborns with malformations, 4 were diagnosed with congenital torticollis, 2 with hypospadias, and 3 with congenital heart defects, yielding a cardiac malformation prevalence of 3% compared with about 1% in the general population.[2]

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These data are important to manage care for individuals who could become pregnant (traditionally, adolescent girls and women from age 15 to 49) who may be prescribed modafinil or armodafinil, predominantly for narcolepsy treatment. Raising the awareness of the medical community and educating individuals who could become pregnant on the high rate of unintended pregnancy—up to 45% in 2011 in the United States[3]—are crucial when considering teratogens, especially in those disparately affected: women 18 to 24 years of age, unmarried/cohabiting, of low income, with an incomplete high school education, and/or of an ethnic or racial minority group.[4]

Given this high rate of unintended pregnancy, individuals who could become pregnant should avoid taking potentially teratogenic medications (eg, modafinil and armodafinil). Medication safety information is important for all individuals who could become pregnant and is readily available from Mothertobaby.org and other similar resources.

When a medication's benefits outweigh its potential teratogenic risks, individuals who could become pregnant should consider using a contraceptive that is reliable, long acting, and reversible (eg, intrauterine device). For individuals who avoid contraception for religious or other reasons, an alternative to modafinil and armodafinil should be prescribed. If an individual being treated with modafinil or armodafinil intends to become pregnant, a preconception consultation with a maternal-fetal specialist should be recommended for counseling on the medication's risks and benefits. If, however, an individual becomes pregnant while being treated with modafinil or armodafinil, a maternal-fetal specialist and/or genetic counselor should be consulted on the risk of congenital anomalies and possible pregnancy termination.

Timely diagnosis of congenital anomalies can be achieved with high-quality ultrasonography examination. First-trimester ultrasonography should be recommended at 11 to 13 weeks (up to 14 weeks),[5] followed by a detailed ultrasonography at 18 to 22[6] weeks, and possibly, a fetal echocardiogram at 18 to 22 weeks.[2] If an anomaly is detected, the patient's obstetric care may require coordination with the maternal-fetal medicine unit and consultation with a pediatric subspecialist. When congenital heart disease is suspected,

delivery at a hospital with a neonatal care unit should be recommended.

Given the risks of these medications and the high rate of unintended pregnancy, we recommend that pregnancy be considered a possibility in all individuals of reproductive age who may be prescribed a potential teratogen. To avoid major congenital malformations associated with modafinil and armodafinil, these medications should be avoided or offered along with a reliable contraceptive to individuals who could become pregnant.

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Correction: This article was corrected on December 14, 2020, to recommend first-trimester ultrasonography be performed up to 14 weeks, not 19 weeks.

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Family Caregiving for Those With and Without Dementia in the Last 10 Years of Life

Family caregivers of people with dementia (eg, spouses, children, and other unpaid caregivers) provide high levels of care[1] and experience substantial caregiver strain at the end of life,[2] yet little is known about the trajectory of care as the end of life approaches and how individual family members contribute to total care. We compared the hours of care that family caregivers provide to those with and without dementia during the last 10 years of life.

Methods | We sampled all decedents in the nationally representative Health and Retirement Study, including interview waves 2006 to 2016, who were 75 years or older at the time of death (n = 5266) and excluded those with significant missing data (n = 1317). Data analysis was conducted between October 2019 and March 2020. We determined each family caregiver's annual care hours using the decedent's self-reported hours of help received with self-care and household activities in the preceding month. We estimated caregiving hours between interviews using a weighted average of hours from each interview and assigned annual prorated hours based on the time from interview to death.[3] We used a clinically validated algorithm[4] to determine dementia status in the interview before death and then stratified results based on marital status. The study was approved by the Mount Sinai School of Medicine institutional review board with a waiver of informed consent due to the retrospective nature of the study.

Results | Family caregivers of people with dementia provided 3 times as many total hours of care over the last 10 years of life compared with caregivers of those without dementia (**Figure**). While care hours provided to those with dementia increased steadily in each of the last 10 years (mean annual increase, 17%; range 18%-41%), care hours provided to those without dementia remained low and then nearly tripled in the last year of life (mean [SD] of 8 [23] hours of care per week 1-2 years before death and 22 [35] hours in the last year of life). Adult children of those with dementia provided a larger portion of total care hours (50%) compared with those without dementia (41%). In the last year of life, adult children of those with dementia provided a mean (SD) of 17 (34) hours of care per week, while children of those without dementia provided a mean (SD) of 10 (22) hours. Among those married at the interview before death, spousal caregivers provided most of the care hours over all 10 years before death in the dementia and nondementia groups (81% and 77% of total care hours, respectively).

Discussion | Our study highlights the high levels of caregiving provided to those with dementia by their family caregivers in general and by adult children in particular. All married individuals relied primarily on spouses to provide care. However, adult children provided the bulk of care for family members with dementia, who were on average older and more likely to be widowed; substantial caregiving responsibilities for this population often began at least 10 years before death.

The survey data did not assess the total time caregivers spent with family members; some time reported as caregiving may have replaced time spent in social engagement before needs arose, and our results may therefore overstate the time spent providing care. However, this limitation is unlikely to explain the many hours spent caregiving for individuals with dementia. Moreover, sustained caregiving responsibilities for individuals with dementia likely have financial implications beyond the time spent providing care. Caregivers may work fewer hours, miss opportunities for advancement, or fail to enter or stay in the workforce[5]; indirect costs of caregiving affect financial security and retirement savings and may even affect opportunities for the next generation.