Assessment of non-cardiac congenital malformations and in utero exposure to modafinil/armodafinil in the Sentinel Distributed Database

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Disclosures

I have nothing to disclose.

Some co-authors on this abstract are employed at organizations which conduct work for government and private organizations including pharmaceutical companies.

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Outline

- Background
- Objectives
- Methods
- Statistical analyses
- Results
- Discussion
- Conclusion

Modafinil/armodafinil background

- PROVIGIL® (modafinil, approved by the U.S. FDA in 1998) and NUVIGIL® (armodafinil, approved by the U.S. FDA in 2007) are wakefulness promoting agents indicated to treat excessive sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work disorder.
- In utero exposure to modafinil/armodafinil has been inconsistently associated with major congenital malformations (MCMs) in observational studies
  - In the ongoing Provigil/Nuvigil Registry as of February 2019, 13% (n = 13) of 102 prospective live births had MCMs, which is above the prevalence of ~3% in the general population (Kaplan et al., 2020)
  - Danish study reported adjusted odds ratios (aORs) of 3.4 (95% CI, 1.2-9.7) when comparing modafinil and methylphenidate and 2.7 (95% CI, 1.1-6.9) when comparing modafinil with unexposed (Damkier & Broe 2020)
  - Study in Norway and Sweden did not observe an association (risk ratio, 0.63; 95% CI, 0.09-4.40) (Cesta et al., 2020)
  - Sentinel Active Risk Identification and Analysis (ARIA) study conducted in 2020 of **cardiac** malformations did not observe an association between modafinil/armodafinil exposure and cardiac malformations

Objective

Rule-out a clinically meaningful risk of non-cardiac malformations after first trimester in utero exposure to modafinil or armodafinil using the Sentinel Active Risk Identification and Analysis (ARIA) system.

Methods

Data Partners	Three large national insurers and Medicaid → all link mothers to infants
Query period	January 1, 2006 to December 31, 2022
Enrollment requirement prior to Delivery Date	391 Days (301 day pregnancy length + 90 day pre-pregnancy exposure assessment period)
Enrollment requirement following Delivery Date	30 days
Exposures and comparators	Modafinil/armodafinil, methylphenidate, amphetamines episode overlapping first trimester or no exposure
Exclusions	Chromosomal abnormalities, known teratogens, high dose vitamin A
Outcome	Any non-cardiac malformation, used algorithm by He et al., 2020
Sensitivity analyses	Urinary malformations, musculoskeletal malformations
Subgroups	Maternal age category (<35, 35-44), number of dispensings (1 vs. 2+)

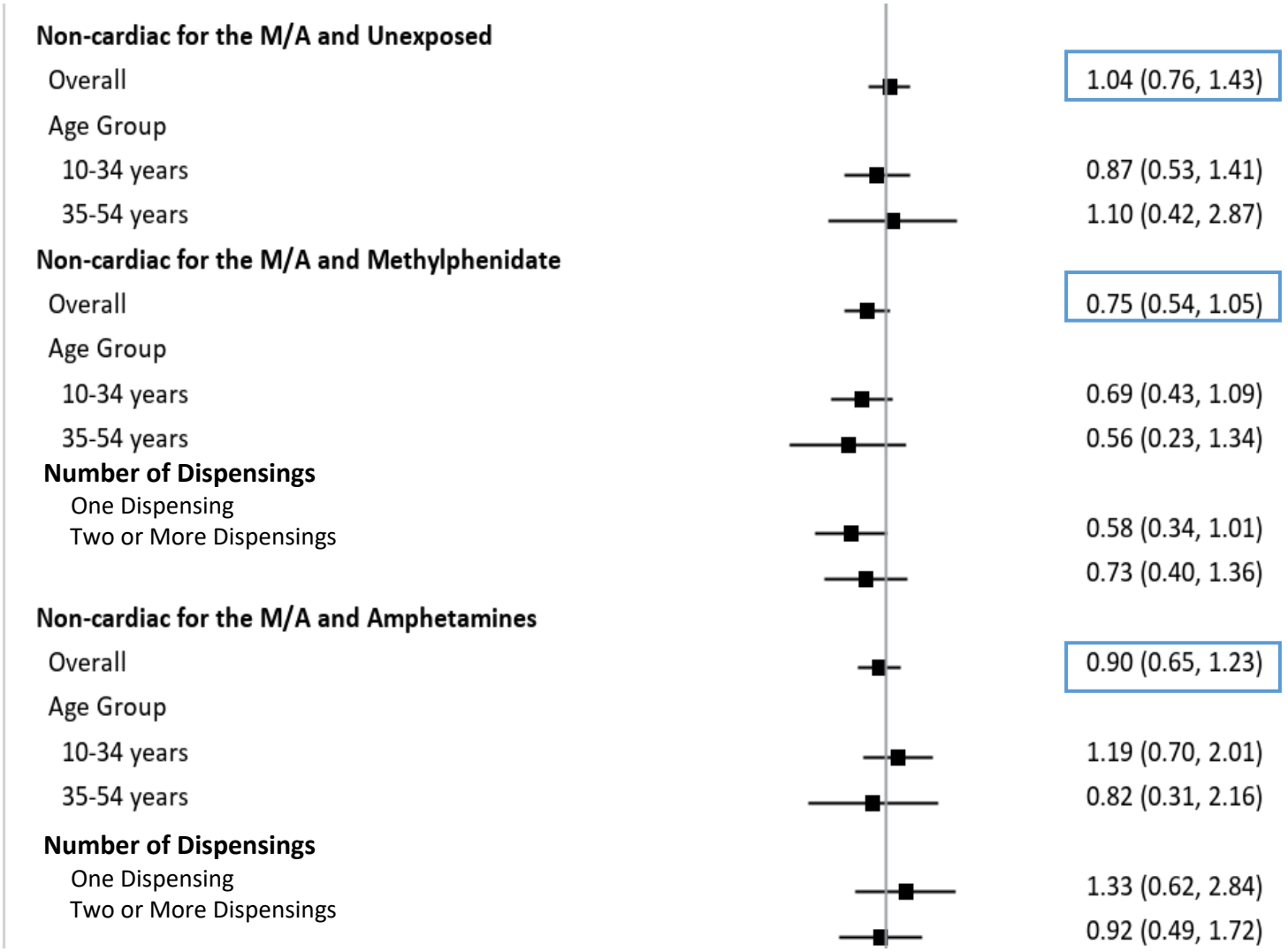
Statistical analyses

- Modafinil/armodafinil exposed pregnancies were compared to referent (amphetamines, methylphenidate, or unexposed) groups matched 1:1 on propensity score.
- For each comparison, we used conditional logistic regression models to estimate odds ratios (OR) and corresponding 95% confidence intervals.

Results

	N		Mean (SD)
	Pregnancies in matched cohorts	Non-cardiac MCM events (%)	Number of dispensings
Armodafinil or modafinil	813	37 (4.6)	1.8 (1.0)
Unexposed	813	40 (4.9)	n/a
Methylphenidate	798	54 (6.8)	2.0 (1.1)
Amphetamines	809	33 (4.1)	2.3 (1.2)

Results: Overall non-cardiac malformations



Odds Ratios (OR) and 95% Confidence Intervals (CI) for Propensity Score Matched Conditional Analyses in the Sentinel Distributed Database from January 1, 2006 to December 31, 2022

Results: Urinary malformations

Risk Estimates for Urinary Malformations for Modafinil or Armodafinil in the Sentinel Distributed Database from January 1, 2006 to December 31, 2022
Fixed Ratio 1:1 Propensity Score Matched Conditional Analysis; Caliper= 0.05

Medical Product	Number of Pregnant Patients	Risk Difference per 1,000 Pregnant Patients	Odds Ratio (95% Confidence Interval)
Modafinil/Armodafinil	813	1.23	1.17 (0.54, 2.53)
Unexposed	813		
Modafinil/Armodafinil	798	2.51	1.50 (0.60, 3.74)
Methylphenidate	798		
Modafinil/Armodafinil	809	2.47	1.50 (0.60, 3.74)
Amphetamines	809		

Number of events are not presented due to a small sample size or to assure a small cell cannot be recalculated through the cells presented

Results: Musculoskeletal malformations

Risk Estimates for Musculoskeletal Malformations for Modafinil or Armodafinil in the Sentinel Distributed Database from January 1, 2006 to December 31, 2022
Fixed Ratio 1:1 Propensity Score Matched Conditional Analysis; Caliper= 0.05

Medical Product	Number of Pregnant Patients	Risk Difference per 1,000 Pregnant Patients	Odds Ratio (95% Confidence Interval)
Modafinil/Armodafinil	813	-3.69	0.73 (0.38, 1.40)
Unexposed	813		
Modafinil/Armodafinil	798	-10.03	0.50 (0.27, 0.92)
Methylphenidate	798		
Modafinil/Armodafinil	809	-1.24	0.89 (0.45, 1.75)
Amphetamines	809		

Number of events are not presented due to a small sample size or to assure a small cell cannot be recalculated through the cells presented

Discussion

- Limitations
  - Residual confounding
    - Unlikely to explain our null results
  - Small sample size for subgroup analyses
    - Specific MCMs could not be assessed
  - Potential exposure and outcome misclassification
- Strengths
  - Large sample size for overall analyses
    - More than ten times the number of events than previous retrospective cohort studies
  - Used a validated outcome for MCMs
    - Positive predictive value of 86% (74%-94%) in the Medicaid database (He et al., 2020)
  - Used two active comparators

Conclusion

Our results do not support an association between in utero exposure to modafinil/armodafinil and non-cardiac MCMs.

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