Ondansetron Use among Pregnancies Identified in the Sentinel Distributed Database

Lockwood G. Taylor, PhD, MPH
Division of Epidemiology
FDA/CDER/OSE

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Disclaimer

- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA.

- No financial conflicts

Background

- Ondansetron is a selective 5HT-3 receptor antagonist approved for prevention of nausea and vomiting (NV) with chemotherapy, radiotherapy, and post-operatively
  - Not approved for NV in pregnancy (NVP) but prescribed off-label
  - Only doxylamine/pyridoxine(Diclegis™, approved 2013) approved for NVP
- Several recent studies suggest an increase in congenital malformations with ondansetron use in early pregnancy; however evidence is inconclusive
- Needed to better understand antiemetic use in a cohort of pregnant women

Objective

- To assess ondansetron use in pregnancy, in the context of other antiemetic use, among a large insured U.S. population of women delivering live births

Methods

- Used pregnancies ending in live birth among women ages 10-54 identified in 15 Sentinel data partners to evaluate antiemetic use in pregnancy, 2001-2015
- Pregnancy identification and gestational age based on validated algorithm[1]
- Assessed all forms of use of the following antiemetics via National Drug Codes:
  - **Ondansetron, metoclopramide, promethazine, doxylamine/pyridoxine,** prochlorperazine, granisetron, dolasetron, palonosetron
- Unable to assess inpatient oral use

[1]Li Q, Andrade SE, Cooper WO, et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. Pharmacoepidemiol Drug Saf 2013;22:524-32.

Methods

- Assessed use by trimester and calendar year
  - Trend analyses only through 2014 since 2015 is partial year of data
  - 1st, 2nd, and 3rd trimesters defined as 0-90 days, 91-180 days, and 181-delivery, respectively
- Not all data partners contributed data over the entire study period; more partners contributing data in more recent years

Results

Table 1. Characteristics of pregnancies ending in live births identified within the Sentinel Distributed Database, 2001-2015[a]

Characteristic (for treatment group)		N(%)
Total unique women with a pregnancy episode		1,949,201 (100.00%)
Total unique pregnancy episodes		2,342,489 (100.00%)
Calendar year of delivery	2001	41,743 (1.78%)
	2002	62,172 (2.65%)
	2003	62,162 (2.65%)
	2004	61,429 (2.62%)
	2005	64,443 (2.75%)
	2006	67,906 (2.90%)
	2007	120,743 (5.15%)
	2008	145,482 (6.21%)
	2009	245,499 (10.48%)
	2010	275,250 (11.75%)
	2011	267,874 (11.44%)
	2012	258,454 (11.03%)
	2013	263,380 (11.24%)
	2014	253,006 (10.80%)
	2015[a]	152,946 (6.53%)
Maternal age at delivery, years	< 20	132,042 (5.64%)
	20-24	318,473 (13.60%)
	25-29	606,107 (25.87%)
	30-34	769,400 (32.85%)
	35-39	411,274 (17.56%)
	40-44	94,740 (4.04%)
	45-54	10,453 (0.45%)
Gestational age category[b]	Preterm	174,162 (7.43%)
	Late/Post-term	333,978 (14.26%)

[a] Not all Mini-Sentinel data partners contributed data for the entire study period; 2015 represents partial year of data

[b] Categories derived from gestational age diagnostic codes given to preterm and late-term/post-term infants

Results

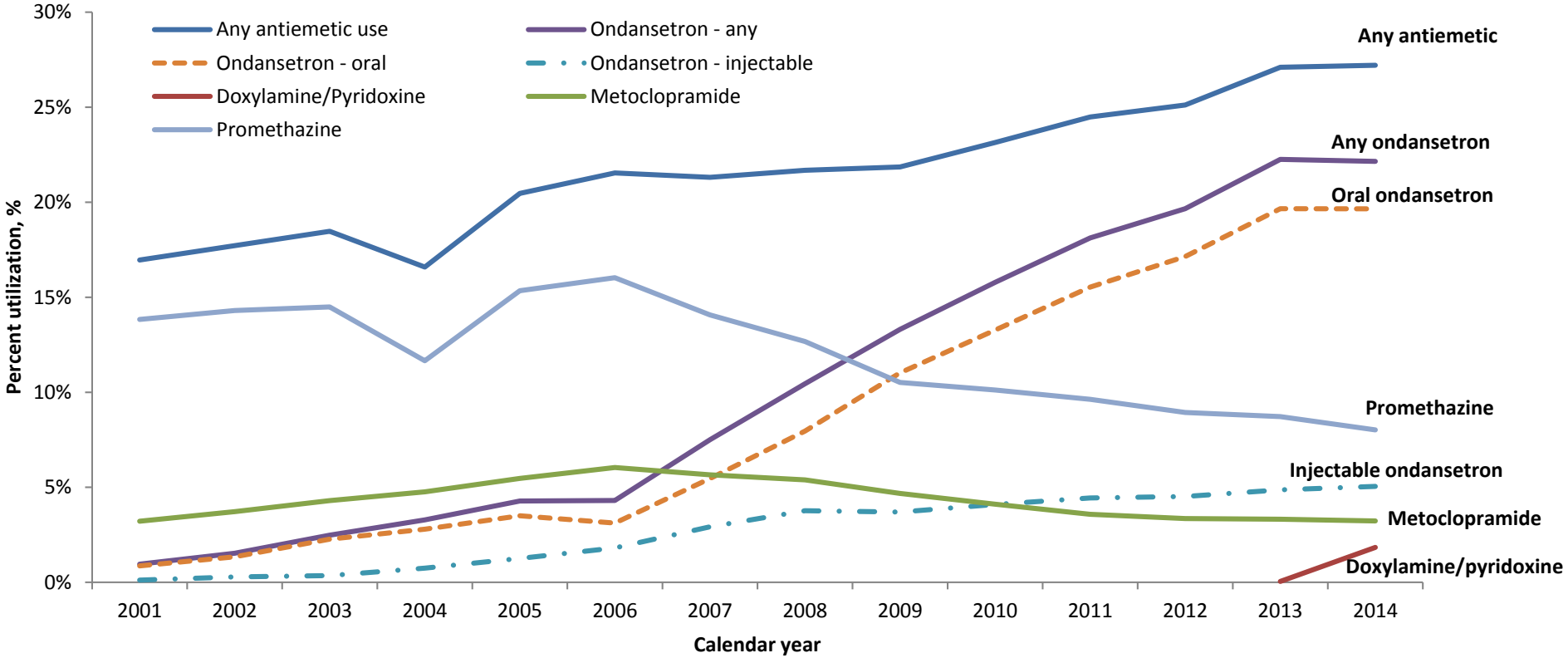
Table 2: Prevalence of antiemetic prescription among live birth pregnancies identified in the Sentinel Distributed Database, 2001-2015[a]

Generic Name[b]	Use in the 90 Days Before Pregnancy	Any Use During Pregnancy	Any Use, First Trimester	Any Use, Second Trimester	Any Use, Third Trimester	Use in First, Second, and Third Trimester
No. pregnancies	n=2,342,489	n=2,342,489	n=2,342,489	n=2,342,489	n=2,341,992[d]	n=2,341,992[d]
Any antiemetic	78,770 (3.36)	550,335 (23.49)	390,217 (16.66)	265,820 (11.35)	157,217 (6.71)	52,453 (2.24)
Dolasetron	346 (0.01)	3,155 (0.13)	2,167 (0.09)	1,568 (0.07)	578 (0.02)	165 (0.01)
Doxylamine/Pyridoxine[c]	30 (0.00)	8,735 (0.37)	6,812 (0.29)	5,943 (0.25)	1,903 (0.08)	1,006 (0.04)
Granisetron	161 (0.01)	352 (0.02)	163 (0.01)	133 (0.01)	123 (0.01)	10 (0.00)
Metoclopramide	9,797 (0.42)	93,481 (3.99)	57,433 (2.45)	38,868 (1.66)	21,615 (0.92)	2,250 (0.10)
Ondansetron	39,775 (1.70)	356,777 (15.23)	255,825 (10.92)	167,490 (7.15)	90,549 (3.87)	29,390 (1.25)
Palonosetron	26 (0.00)	101 (0.00)	16 (0.00)	55 (0.00)	74 (0.00)	2 (0.00)
Prochlorperazine	3,173 (0.14)	16,500 (0.70)	10,263 (0.44)	6,070 (0.26)	2,719 (0.12)	185 (0.01)
Promethazine	37,115 (1.58)	240,748 (10.28)	158,275 (6.76)	92,380 (3.94)	63,774 (2.72)	13,266 (0.57)

[a] Not all Mini-Sentinel data partners contributed data for the entire study period; 2015 represents partial year of data
[b] All formulations included (injectable, oral, rectal)
[c] Approved in 2013
[d] Total number of pregnancies is lower for third trimester exposure since some live births occurred in late the second trimester

Results

Figure 1: Utilization of antiemetic drugs among live birth pregnancies by calendar year in the Sentinel Distributed Database, 2001-2014[a,b]



[a] Dashed lines for oral and injection ondansetron form represent a portion of all total ondansetron use as shown by the solid purple line. Summation of oral and injection utilization sums to greater than total ondansetron use since some women received both products.
[b] Not all Mini-Sentinel data partners contributed data for the entire study period

Discussion

- We observed a marked increase in ondansetron use by calendar year, occurring in conjunction with decreased use of promethazine and metoclopramide
  - Increase largely driven by oral formulation
  - Similar trend across all data partners
- Ondansetron was prescribed to nearly 1 in 4 insured pregnant women captured in Sentinel in 2014
- Why the increase?
  - Unclear, but large number of approved generic applications in 2006 and 2007 and relaxed prior authorization policies in some health care systems may explain part of increase
    - 20 generic applications for oral ondansetron; 19 for injectable
  - Ondansetron not recommended as first-line pharmacotherapy in 2004 and 2015 Practice Bulletins[1,2]

[1]Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol 2015;126:e12-24.
2Practice Bulletin No. 52: Nausea and Vomiting of Pregnancy. Obstet Gynecol 2004: 103(4): 803-815.

Conclusion

- Given the widespread use of ondansetron in pregnancy, a great need exists for data establishing its efficacy as well as methodologically rigorous post-marketing assessments to evaluate its safety in pregnant women.

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Study team

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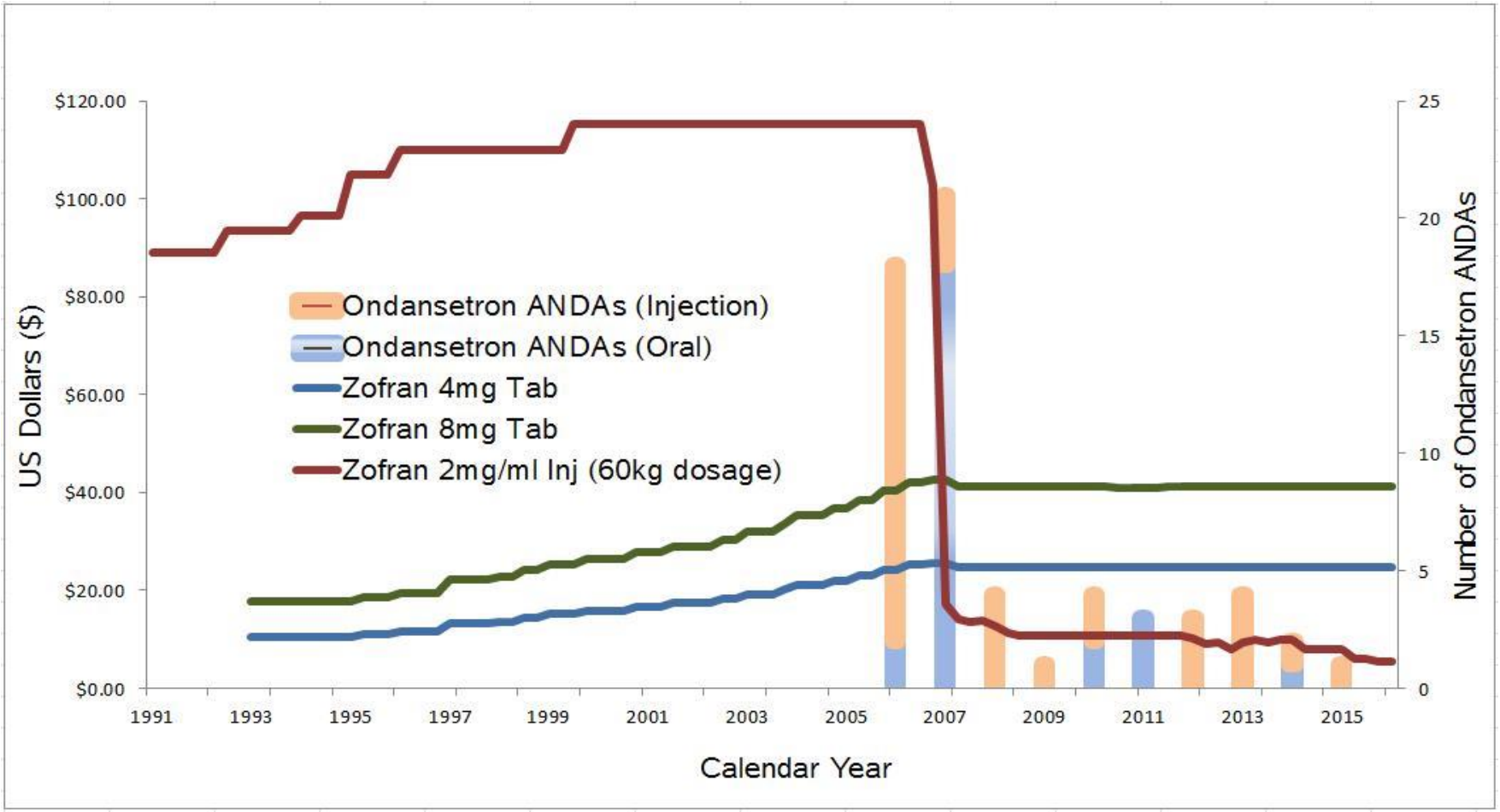
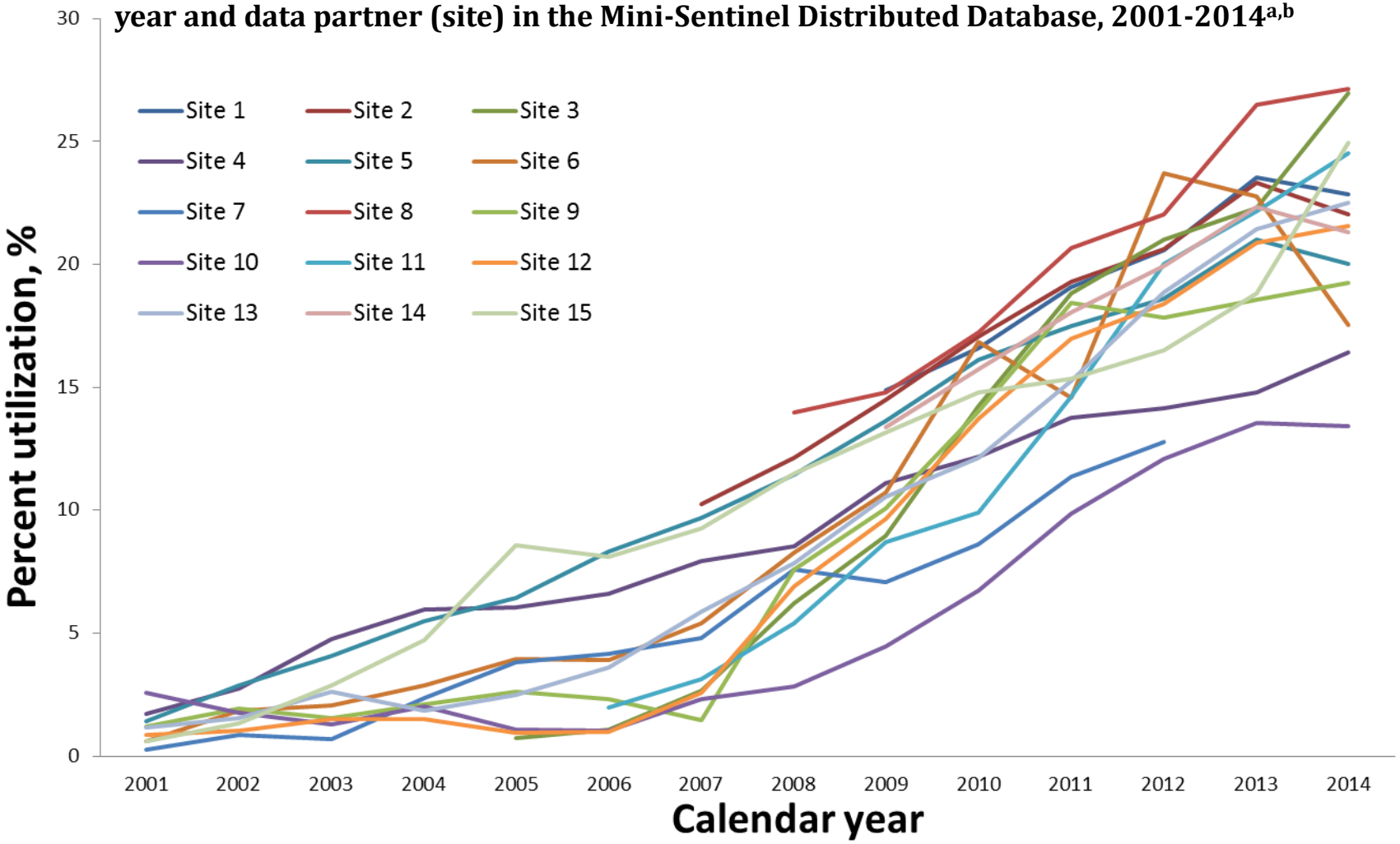
Back-up slides

Figure 1: Median Average Wholesale Price (AWP) of ondansetron in US dollars by formulation overlaid with number of new ANDAs[a] by calendar year[b,c]



[a]ANDA (Abbreviated New Drug Application): FDA approved generic products. [b]AWP information obtained from Red Book Online [database online]. Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Updated 2016. Accessed February 4, 2016. [c]ANDA information obtained from Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations Online [database online]. Updated March 2016. Accessed March 3, 2016.

Figure 2: Utilization of ondansetron (all forms) among live birth pregnancies by calendar year and data partner (site) in the Mini-Sentinel Distributed Database, 2001-2014[a,b]



[a]Not all Mini-Sentinel data partners contributed data for the entire study period. [b]Site 6 contributed smaller numbers of pregnancies to the analysis which contributed to the relatively unstable trend in prevalence of ondansetron use.