Utilization of beta-blockers among the pediatric population in the United States: a study in the FDA's Sentinel System from 2008 to 2022

Yan Li[1], Meg Her[2], Efe Eworuke[3], Mohamed Mohamoud[1], José J. Hernández-Muñoz[1], Ivone Kim[1], Jennifer W. Thompson[2], James W. Antoon[4], John G. Connolly[2]

1. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA
2. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
3. Epidemiology and Drug Safety, IQVIA Real World Solutions 4. Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA

Background

- Oral formulations of beta-blockers are only approved for two pediatric indications in the United States (i.e., hypertension and infantile hemangioma), but are commonly used for a variety of off-label conditions.
- In addition to concerns for lack of efficacy, such use may be associated with increased risk of adverse events and medication errors.
- Compared to adults, little is known about the magnitude and patterns of beta blocker use in the pediatric population.

Objectives

- To examine utilization patterns of beta-blockers among the pediatric population in the United States, including the prevalence of use and user characteristics.

Methods

- **Data source**: administrative claims data and electronic health records from eight Data Partners of FDA's Sentinel System from Jan 2008 to May 2022.
- **Study population**: beneficiaries <18 years of age who were enrolled in health plans with medical and drug coverage for at least 1 day (to identify prevalent users) or 183 days (to identify incident users; for infants less than 6 months of age, continuous medical and drug coverage was required since birth).
- **Beta blockers of interest** included oral formulations of acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, sotalol, and timolol.
- **The prevalence of beta blocker use** was calculated by dividing the number of children who filled at least one beta blocker prescription by the number of eligible children. We reported prevalence overall, by sex, by age group, by individual beta blocker, and by calendar year. For the calendar year stratified analysis, we calculated age- and sex-standardized prevalence using the direct method based on the U.S. Census population of 2021 to account for the changing underlying population in the data source.
- **User characteristics** were determined among incident beta blocker users (no dispensing in the preceding 183 days or no dispensing since birth for infants under six months of age). Potential indications of use were assessed during a **90-day look back window** before the first dispending.

Results

- Our study included 89,753,239 eligible children, among whom there were 279,039 prevalent users (prevalence: 3.11 per 1000) of beta blockers.
- As shown in **Table 1**, the age- and sex-standardized prevalence of beta blocker use increased by more than 50% (prevalence ratio: 1.54) from 2008 to 2021. This increase was more pronounced among females than males.
- There was a notable increase in use for the age group 0-1 year, and a moderate increase for the age group 13-17 years. The use among the age groups 2-5 years and 6-12 years remained relatively constant.
- Propranolol accounted for the majority of use. The prevalence of its use increased by about 140%. There was a prominent increase in the use of the newly introduced propranolol (Hemangeol) oral solution.

Table 1. Trends in the Use of Beta-Blocker among the Pediatric Population in the Sentinel System

	Prevalence per 1,000														Prevalence ratio
Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	
Prevalence	1.24	1.30	1.33	1.41	1.46	1.51	1.49	1.53	1.58	1.58	1.66	1.91	1.84	2.04	1.65
Standardized prevalence*	1.17	1.21	1.24	1.31	1.35	1.38	1.43	1.50	1.55	1.54	1.59	1.72	1.64	1.80	1.54
Female	1.38	1.45	1.48	1.60	1.66	1.74	1.69	1.76	1.83	1.82	1.93	2.40	2.32	2.68	1.94
Male	1.11	1.15	1.18	1.22	1.26	1.29	1.30	1.31	1.34	1.35	1.39	1.45	1.38	1.43	1.29
Age 0-1 year	0.39	0.53	0.74	0.90	0.99	1.07	1.08	1.14	1.16	1.21	1.33	1.65	1.87	2.10	5.44
Age 2-5 years	0.25	0.24	0.26	0.29	0.28	0.30	0.31	0.34	0.34	0.34	0.36	0.34	0.32	0.31	1.23
Age 6-12 years	0.81	0.79	0.77	0.81	0.79	0.80	0.86	0.88	0.88	0.86	0.87	0.79	0.74	0.76	0.94
Age 13-17 years	2.57	2.70	2.72	2.82	2.96	3.04	3.10	3.27	3.44	3.39	3.52	3.97	3.71	4.15	1.61
Propranolol	0.63	0.67	0.71	0.78	0.83	0.88	0.91	0.93	0.98	1.00	1.08	1.31	1.28	1.49	2.36
Hemangeol*							0.004	0.01	0.02	0.02	0.02	0.04	0.05	0.07	16.48
Atenolol	0.33	0.34	0.33	0.33	0.31	0.33	0.29	0.31	0.30	0.27	0.24	0.26	0.24	0.24	0.83
Metoprolol	0.15	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.16	0.17	0.18	0.16	0.16	1.09
Nadolol	0.07	0.08	0.09	0.10	0.10	0.11	0.08	0.07	0.07	0.07	0.07	0.10	0.10	0.10	1.40

*Hemangeol, an oral solution of propranolol, was particularly approved for infantile hemangioma in the United States in 2014

- As shown in **Table 2**, a total of 200,926 unique patients contributed 214,231 incident use episodes. There were more females (60.5%) than males in this sample. The majority of incident users were 13-17 years (64.4%), followed by the 6-12 years (19.3%), 0-1 year (13.4%), and 2-5 years (3.0%). The most commonly used beta blockers were propranolol (68.8%), atenolol (14.3%), and metoprolol (8.5%).
- The most common potential indications of use were anxiety disorder (21.8%), migraine (21.2%), cardiac arrhythmias (17.6%), congenital heart disease (8.5%), hemangioma (7.3%), and hypertension (6.9%).
- There was a noteworthy shift in potential indications for beta blocker use across different age groups. Among younger children, most of the use was for cardiac conditions, while among older children, most of the use was for non-cardiac conditions.

Table 2. Characteristics of Incident Beta-Blocker Users in the Sentinel System (Overall, by Age, and by Sex)

Characteristics	Overall cohort	0-1 year	2-5 years	6-12 years	13-17 years	Female	Male
Unique patients	200,926	28,248	6,090	39,081	129,931	121,477	79,449
Episodes	214,231	28,621	6,366	41,380	137,864	129,557	84,674
Mean Age ± SD	12.5±5.6	0.4±0.4	4.2±1.2	10.4±1.9	16.0±1.3	12.9±5.6	11.9±5.7
0-1 year	13.4%	100%				12.8%	14.2%
2-5 years	3.0%		100%			2.3%	3.9%
6-12 years	19.3%			100%		15.5%	25.1%
13-17 years	64.4%				100%	69.3%	56.8%
Female	60.5%	58.1%	47.6%	48.8%	65.0%	100%	
Any Propranolol	68.8%	90.1%	50.0%	62.0%	67.2%	71.0%	65.3%
Propranolol ER	7.6%	N/A	0.3%	5.5%	10.1%	8.1%	6.8%
Propranolol IR	60.2%	81.7%	48.9%	56.7%	57.3%	61.7%	57.9%
Hemangeol	1.1%	8.4%	0.8%	N/A	0.0%	1.4%	0.8%
Atenolol	14.3%	3.8%	26.0%	21.2%	13.9%	13.2%	16.0%
Any metoprolol	8.5%	0.8%	5.9%	7.0%	10.6%	7.8%	9.6%
Metoprolol ER	4.8%	0.2%	2.0%	3.7%	6.2%	4.4%	5.4%
Nadolol	3.0%	0.2%	4.6%	4.9%	2.9%	2.8%	3.2%
Labetalol	2.3%	0.6%	3.9%	1.6%	2.8%	2.9%	1.4%
Carvedilol	1.9%	2.6%	7.3%	2.2%	1.4%	1.2%	2.9%
Acebutolol	0.0%	N/A	N/A	0.1%	0.0%	0.0%	0.0%
Sotalol	0.5%	2.0%	1.7%	0.3%	0.2%	0.3%	0.7%
Bisoprolol	0.3%	N/A	0.3%	0.2%	0.3%	0.3%	0.3%
Nebivolol	0.3%	N/A	0.2%	0.2%	0.3%	0.2%	0.3%
Betaxolol	0.1%	0.0%	N/A	0.1%	0.1%	0.1%	0.1%
Pindolol	0.1%	0.0%	N/A	0.1%	0.2%	0.1%	0.1%
Timolol	0.0%	0.0%	N/A	N/A	0.1%	0.0%	0.0%

Table 2 continued. Characteristics of Incident Beta-Blocker Users in the Sentinel System (Overall, by Age, and by Sex)

Characteristics	Overall cohort	0-1 year	2-5 years	6-12 years	13-17 years	Female	Male
Anxiety Disorder	21.8%	0.1%	3.5%	14.8%	29.2%	24.3%	18.0%
Migraine	21.2%	0.1%	6.6%	26.3%	24.7%	24.1%	16.7%
Cardiac Arrhythmia	17.6%	30.1%	32.9%	17.3%	14.4%	16.1%	20.0%
Congenital Heart Disease	8.5%	36.3%	20.5%	6.7%	2.7%	6.4%	11.6%
Hemangioma	7.3%	52.5%	6.5%	0.3%	0.1%	8.7%	5.2%
Hypertension	6.9%	4.4%	11.5%	6.0%	7.4%	5.1%	9.5%
Autism	3.3%	0.0%	3.6%	6.5%	3.0%	1.3%	6.4%
Thyrotoxicosis	2.6%	0.3%	3.5%	3.3%	2.9%	3.4%	1.5%
Tremor	1.9%	0.2%	1.4%	1.3%	2.4%	1.6%	2.2%
Cardiomyopathy	1.7%	3.7%	4.9%	1.9%	1.1%	1.1%	2.6%
Heart Failure	1.5%	5.6%	4.9%	1.2%	0.6%	1.1%	2.1%
Pulmonary Hypertension	0.6%	2.8%	1.5%	0.3%	0.2%	0.4%	0.8%
Coronary Artery Disease	0.4%	0.7%	0.9%	0.4%	0.3%	0.3%	0.6%
Marfan's Syndrome	0.4%	0.2%	2.1%	0.9%	0.3%	0.3%	0.7%
Burns	0.2%	0.3%	1.2%	0.3%	0.2%	0.2%	0.3%
Glaucoma	0.2%	0.1%	0.2%	0.3%	0.2%	0.2%	0.2%
Portal Hypertension	0.1%	0.2%	0.8%	0.2%	0.1%	0.1%	0.2%
Pheochromocytoma /Paraganglioma	0.1%	0.2%	0.4%	0.1%	0.0%	0.1%	0.1%
Any of the above health characteristics	72.2%	91.1%	72.8%	68.6%	69.3%	72.7%	71.5%
None of the above health characteristics	27.8%	8.9%	27.2%	31.4%	30.7%	27.3%	28.5%

ER: extended release; IR: immediate release; SD: standard deviation
N/A: data were not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented

Conclusion

- Beta-blockers were used for a variety of cardiac and non-cardiac conditions in the pediatric population and characteristics of users differed significantly between age groups. In recent years, there was a notable increase in their use among the age group 0-1 year. More evidence is needed to support the efficacy and safety of beta-blocker use in the pediatric population.

Acknowledgements: Many thanks are due to the Sentinel Data Partners who provided data used in the analysis.

Disclaimer: This project was supported by Task Order 75F40119F19001 under Master Agreement 75F40119D10037 from the U.S. Food and Drug Administration (FDA). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government. Efe Eworuke was an employee of FDA during the time of study conduct. She is now employed by IQVIA. Other authors have no conflicts of interest to disclose.

Contact: yan.li@fda.hhs.gov