

# Epinephrine Autoinjector Prescribing Trends: An Outpatient Population-Based Study in Olmsted County, Minnesota



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**What is already known about this topic?** The prescription trend of epinephrine autoinjector can be an indicator of the prevalence of patients who have experienced or are at risk of anaphylaxis.

**What does this article add to our knowledge?** The incidence rate of epinephrine autoinjector prescriptions increased from 2004 to 2010. In childhood, boys were more likely to receive a prescription than girls, but this reversed in later ages.

**How does this study impact current management guidelines?** Rates of increased epinephrine autoinjector may be related to increased burden of allergic disease, especially food allergy in young patients, increased public awareness, as well as increasing recognition and frequency of diagnosis by health care providers.

**BACKGROUND:** The prescribing pattern of epinephrine over time is an indicator of the secular trend of anaphylaxis. However, it is not well known in a population level in the United States. **OBJECTIVE:** To evaluate the trend of prescriptions for epinephrine autoinjectors in Olmsted County, Minn, residents. **METHODS:** Outpatient prescriptions for epinephrine were identified among residents of Olmsted County, Minn, between January 1, 2004, and December 31, 2010. We used the first prescription per patient per year, and the first prescription per patient during the study period to calculate incidence rates. Incidence rates per 100,000 person-years were calculated using patients prescribed epinephrine per year as the numerator and age- and sex-specific counts of the population of Olmsted

County as the denominator. The relationships of age group, sex, and year of prescription with incidence rates were assessed by fitting Poisson regression models using the SAS procedure GENMOD.

**RESULTS:** The overall incidence rate of epinephrine autoinjector prescriptions during the study period was 757 per 100,000 person-years (95% confidence interval: 740-774). The prescription rates per patient per year increased over time, with an annual rate of increase of 8% ( $P < .001$ ), but the rates per patient remained stable ( $P = .077$ ). For each year, incidence rates overall were higher in women compared with men ( $P < .001$ ). From ages 0 to 19, incidence rates were higher in boys compared with girls. At age 20 and above, incidence rates were higher in women compared with men.

**CONCLUSIONS:** The overall rate of epinephrine autoinjector prescriptions increased, but the rate of first-time prescriptions was stable from 2005 to 2010. In childhood, boys were more likely to receive a prescription than girls, but this reversed in later ages. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1182-6)

**Key words:** Anaphylaxis; Epinephrine autoinjector; Epidemiology; Incidence rate

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*Abbreviations used*

REP- Rochester Epidemiology Project  
CI- Confidence interval  
ED- Emergency department

medical care in Olmsted County, Minn.<sup>4-7</sup> Prescription data have become available as a part of the REP since 2003.<sup>8</sup> Thus, evaluating trends of prescribing for epinephrine autoinjectors within the REP will provide an additional method of estimating the prevalence of patients who have experienced or are at risk of anaphylaxis in Olmsted County, Minn.

In this study, we used the REP research infrastructure to determine the trends of epinephrine autoinjector prescriptions in Olmsted County residents over a 7-year period, 2004-2010. We hypothesized that the number of prescriptions per year would increase, suggesting an increasing prevalence of anaphylaxis in Olmsted County, Minn.

**METHODS**

**Study population**

All Olmsted County residents identified by REP census between January 1, 2003, and December 31, 2010, who had given permission for their medical records to be used for research were included in the study. A previous study showed that the record linkage system through the REP captures 98.7% of the population of Olmsted County by US census, and the age and sex distributions were nearly identical to US census estimates.<sup>9</sup> The prescription data capture above 80%-90% from Mayo Clinic and Olmsted Medical Center, 2 large health care organizations in Olmsted County. A previous study suggested that some noncritical medications may be undercounting but still accurately describe trends.<sup>8</sup> St Sauver et al<sup>9</sup> reported that age, sex, and ethnic characteristics of Olmsted County were similar to those of the state of Minn and the Upper Midwest; however, Olmsted County was less ethnically diverse than the entire US population, more highly educated, and wealthier. Additional details of REP studies have been published elsewhere.<sup>9-12</sup> The study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center.

**Prescription records**

Outpatient prescriptions between January 1, 2003, and December 31, 2010, were obtained from the Mayo Clinic and Olmsted Medical Center in Rochester Minn. These 2 institutions provide nearly all of the health care for Olmsted County residents.<sup>9,10,12</sup> Both institutions use electronic prescription systems in outpatient settings. Epinephrine autoinjectors were available in 29 prescription formularies. All prescriptions were mutually exclusive, and individuals who received multiple prescriptions within available formularies were counted only once per year for each year during the study period, and first-time prescriptions were also counted once per patient for each year, and once per patient during the study period. We counted each prescription only once whether it was for a single autoinjector or 2-pak. We did not account for refills or duration of medication use.

**Statistical analysis**

First, we selected the first prescription per patient per year to estimate incidence, and then described first prescription per patient during the study period. Trends for first-time prescriptions were analyzed from 2004 to 2010 to allow for a 1-year washout period to be able to account for patients who had received a prescription the year before. Prescriptions in 2003 were removed to account for a

washout period during the first 12 months of the study. Incidence rates per 100,000 person-years were calculated using patients prescribed epinephrine as the numerator, and age- and sex-specific counts of the population of Olmsted County as the denominator. The denominators were obtained from a complete enumeration of the Olmsted County population provided by the REP.<sup>13</sup> Because the population of Olmsted County is nearly all white, incidence rates were directly age- and sex-adjusted to the structure of the 2010 US white population. Patients were grouped by age into those 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, and 60+ years old.

The relationships of age group, sex, and year of prescription with incidence rates were assessed by fitting Poisson regression models using the SAS procedure GENMOD. Statistical analyses were performed using version 9.3 of the SAS software package (SAS Institute, Cary, NC). All hypothesis tests were 2-sided, and *P* values < .05 were considered statistically significant.

**RESULTS**

**Overall findings**

A total of 7991 prescriptions among 3801 patients from 2004 to 2010 were identified in Olmsted County. The mean age at the first prescription per year was 31.5 years (median 30 years; interquartile range 11-50; range 0-97). Table I shows the number of prescriptions each year and the demographics of the

**TABLE I.** Summary and demographic characteristics of patients receiving epinephrine autoinjector prescriptions in Olmsted County, Minn, from January 1, 2004, to December 31, 2010 (N = 7991)

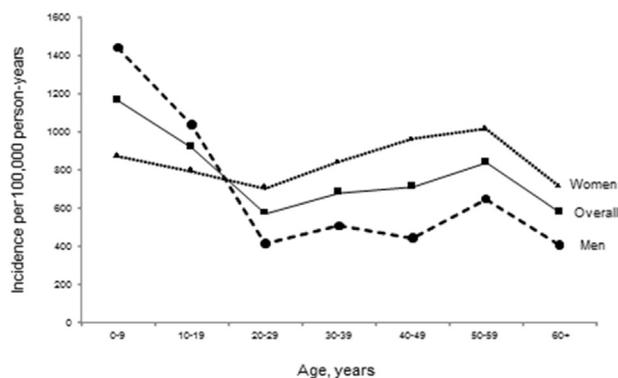
Feature	N (%)
Age (y)	
0-9	1752 (22)
10-19	1277 (16)
20-29	930 (12)
30-39	952 (12)
40-49	1069 (13)
50-59	1068 (13)
60+	943 (12)
Sex	
Female	4488 (56)
Male	3503 (44)
Race	
Black	213 (3)
Asian	349 (4)
Hawaiian/Pacific Islander	16 (<1)
American Indian	19 (<1)
Other/mixed	358 (4.5)
Undisclosed	98 (1)
White	6938 (87)
Year	
2004	819 (10)
2005	918 (11)
2006	1121 (14)
2007	1168 (15)
2008	1231 (15)
2009	1290 (16)
2010	1444 (18)

**TABLE II.** Rates of epinephrine autoinjector prescriptions by age

Age (y)	Women		Men		Both	
	N	Rate*	N	Rate*	N	Rate†
0-9	641	875	1111	1445	1752	1167
10-19	543	796	734	1041	1277	921
20-29	625	709	305	417	930	577
30-39	604	947	348	512	952	684
40-49	749	966	320	445	1069	716
50-59	676	1018	392	650	1068	843
60+	650	720	293	409	943	582
Total	4488	841	3503	664	7991	757

\*Rates per 100,000 person-years age-adjusted to 2010 US white population.

†Rates per 100,000 person-years age- and sex-adjusted to 2010 US white population.

**FIGURE 1.** Rates of self-injectable epinephrine prescriptions overall and by age and sex.

patients who received the prescriptions. The greatest number of prescriptions were written for persons aged 0-9 years, followed by 10-19 years. Table E1 (available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) shows the number of prescriptions per patient for each year. Seven hundred and twenty-five patients had 1 prescription in 2004; 80 patients had 2 prescriptions although only the first one was analyzed. There does appear to be an increase in the proportion of patients with more than 1 prescription during the course of a year ( $P < .001$ ). In 2004, 11% of the patients had more than 1 prescription compared with 17% in 2010. Women received 56% of prescriptions overall. The overall age- and sex-adjusted incidence rate for this analysis was 757 per 100,000 person-years (95% confidence interval [CI]: 740-774). Age-adjusted rates for women and men were 841 (95% CI: 816-866) and 664 (95% CI: 642-689) per 100,000 person-years, respectively.

### Prescription rate by age and sex

Incidence rates by age are summarized in Table II and shown in Figure 1. Incidence rates differed by age group ( $P < .001$ ) and by sex ( $P < .001$ ), and increased over time ( $P < .001$ ). The highest prescription rate was among boys aged 0-9 years. Prescription incidence rates were higher in boys aged 0-19 years compared with girls; however, after age 19, incidence rates were higher in women compared with men.

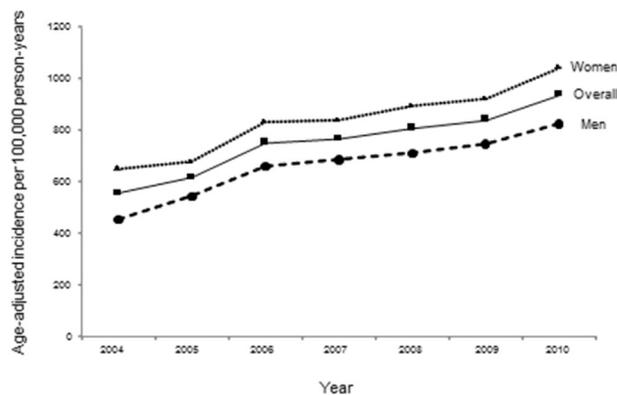
Incidence rates by year are summarized in Table III and shown in Figure 2, and incidence rates of first-time prescriptions

**TABLE III.** Epinephrine autoinjector prescription rates by year

Year	Women		Men		Both	
	N	Rate*	N	Rate*	N	Rate†
2004	483	650	336	454	819	555
2005	510	679	409	545	918	616
2006	625	832	496	659	1121	751
2007	650	840	518	686	1168	767
2008	687	895	544	712	1231	808
2009	716	923	574	746	1290	840
2010	817	1043	627	825	1444	939

\*Rate per 100,000 person-years age-adjusted to 2010 US white population.

†Rate per 100,000 person-years age- and sex-adjusted to 2010 US white population.

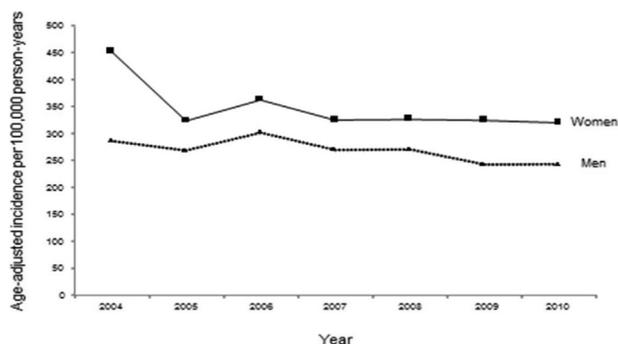
**FIGURE 2.** Rates of self-injectable epinephrine prescriptions overall and by sex, 2004-2010.

during the study period in Figures 3 and 4. Over the study period, there was a 69% increase in the rate of prescriptions from 555 to 939 per 100,000 person-years. The incidence rate ratio for the trend of incidence rates over time was 1.080 (95% CI: 1.068-1.092), indicating that rates increased by 8.0% per year (Figure 2). The overall prescription rate increased in all age groups from 2004 to 2010 ( $P < .001$ ). There was no evidence of a statistically significant difference in the rates of increase between different age groups ( $P = .17$ ). First-time prescription rate decreased during 2004-2010 ( $P < .001$ ), otherwise relatively stable ( $P = .077$ ) from 2005 to 2010, yet there was evidence that incidence rates differed by age group ( $P < .001$ ), differed by sex ( $P < .001$ ) (Figures 3 and 4). Women received more prescriptions than men throughout the study period (Figure 3). Men received more prescriptions than women up to age 19, but this reversed in the older age (Figure 4).

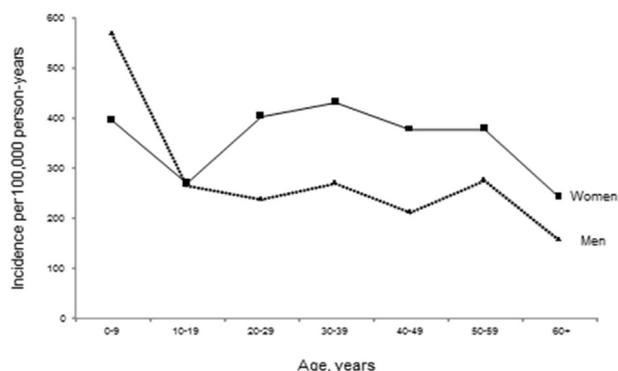
## DISCUSSION

### Statement of principle findings

The overall age- and sex-adjusted incidence rate for this population of patients in Olmsted County, Minn, was 757 per 100,000 person-years. Although, overall, the rate of prescriptions was higher in women than in men, prescription rates were higher in boys aged 0-19 years compared with girls. There was an approximately 8% increase in prescription rates each year over the 7-year study period. However, first-time prescriptions per patient during the study period remained relatively stable.



**FIGURE 3.** The incidence rate of first-time self-injectable epinephrine prescriptions overall and by sex, 2004-2010.



**FIGURE 4.** The incidence rate of first-time epinephrine prescriptions by age and sex.

### Strengths and limitations

The primary strength of our study is the ability to obtain a population-based estimate of epinephrine autoinjector prescriptions over a 7-year period. Through the REP collaborations within Olmsted County, we were able to identify above 80%-90% of all the prescriptions from Mayo Clinic and Olmsted Medical Center, 2 large health care organizations in Olmsted County from 2004 to 2010. Prescription data can be used to help delineate trends of anaphylaxis care and infer anaphylaxis incidence rates.

Our study has several potential limitations. First, the study was conducted in a predominantly white community, and the study findings may not generalize to other more diverse settings. Second, prescription data were available for outpatients including those given at the time of discharge from hospital or emergency department (ED); however, we were unable to estimate the use of an epinephrine autoinjector in the inpatient setting. Furthermore, we were unable to determine the type of provider who provided the prescription such as an allergist and/or immunologist, primary care provider, or ED provider. Third, our prescription data are not linked to the prescriber, and therefore we are not able to describe prescribing trends among different specialties. Fourth, we were not able to capture prescriptions that were called in or handwritten. However, we estimate that these would represent a small proportion of the prescriptions. Fifth, the prescription data do not include dispensing or insurance coverage information. Sixth, the prescription data do not have an

overall trend of other prescriptions, and it is not certain that the trend increase in epinephrine prescription is unique, or it possibly mirrors a general rise in all-cause prescriptions over the period. It is noteworthy that prescriptions for epinephrine autoinjectors written for prophylaxis among patients taking omalizumab could potentially confound the findings. However, only 30 patients during the study period were prescribed omalizumab, and 19 of these patients were also prescribed epinephrine. Therefore, we believe that 19 patients, or 0.5% of the cohort, are unlikely to confound our results. Finally, epinephrine prescriptions do not necessarily indicate treatment of anaphylaxis, as clinicians often prescribe epinephrine to address potential exposure to inciting triggers rather than clinical signs or symptoms.

### Interpretation of findings

To our knowledge, this is the first population-based study to address the trends of epinephrine autoinjector prescriptions in the United States over time. For each year of the study period, rates of epinephrine autoinjector prescriptions were higher in women overall compared with men. The highest rates were observed among patients aged 0-9 years during which boys received more prescriptions than girls. However, women received more prescriptions than men in the older age groups. These findings are consistent with the findings of Simon et al,<sup>3</sup> who studied the population of Manitoba, Canada, from 1995 to 2000. Our demographic findings for epinephrine autoinjectors are also consistent with the demographics observed in prior epidemiological studies of anaphylaxis.<sup>4,14-16</sup> Overall, we found that epinephrine autoinjector prescription rates were higher in women, which is consistent with findings by Decker et al,<sup>4</sup> who reported that overall rates of anaphylaxis were higher in women than in men. Mulla and Simon<sup>15</sup> reported a finding of higher hospitalization among women than men with anaphylaxis in Florida. Our study showed a higher rate of epinephrine autoinjector prescriptions for boys aged 0-9 compared with girls and higher rates in women over age 20 compared with men. Similar trends have been demonstrated in studies of anaphylaxis-related hospitalizations.<sup>14-16</sup> Another study from Australia demonstrated that more boys were hospitalized than girls for angioedema, urticaria, and anaphylaxis, but this reversed in older ages.<sup>16</sup> A higher rate of anaphylaxis hospitalization for males under 20 years of age was also reported in the United States.<sup>14</sup>

Incidence rates of prescription were adjusted for population counts by definition. Taken together, the consistency of our findings with extant literature suggests that epinephrine autoinjectors can be used to estimate the burden of anaphylaxis in a population.<sup>4,17,18</sup>

Lastly, our study showed that the prescription rate increased 8% per year during the study period (69% increase overall), yet the rate of first-time prescription in our cohort during the study period was relatively stable. Pharmacy data from Australia showed a 300% increase in epinephrine autoinjector prescriptions from 1998 to 2002.<sup>19</sup> A study from Israel also showed that epinephrine autoinjector prescriptions increased by 76% from 1997 to 2004.<sup>20</sup> Similarly, national health care data from the United Kingdom showed a 97% increase in epinephrine autoinjector prescriptions along with increased diagnoses of anaphylaxis between 2001 and 2005.<sup>21</sup> These studies reported the crude rate of prescriptions. Thus, our data are consistent with worldwide trends showing increasing rates of epinephrine

autoinjector prescriptions, which reflects the increasing prevalence of anaphylaxis. The findings of a relatively constant trend for first-time prescriptions during the study period suggest that providers are providing refills of epinephrine prescriptions although it is unknown whether newly diagnosed cases of anaphylaxis patients are receiving necessary prescriptions.

## CONCLUSIONS AND FUTURE DIRECTIONS

Outpatient prescriptions of epinephrine autoinjectors showed an overall increase in all age groups from 2004 to 2010 in Olmsted County. However, first-time prescriptions per patient during the study period remained relatively stable. Rates of increase may be related to increased burden of allergic disease, especially food allergy in young patients, increased public awareness, as well as increasing recognition and frequency of diagnosis by health care providers. Further studies are needed to clearly determine if these trends continue and the appropriateness of epinephrine autoinjector prescribing patterns.

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**TABLE E1.** Number of prescriptions per patient, from 2004 to 2010

Year	No. of prescriptions per patient					
	1	2	3	4	5	6
2004	725	80	11	2	1	0
2005	805	99	11	2	0	1
2006	997	110	13	1	0	0
2007	1015	133	17	3	0	0
2008	1094	119	15	3	0	0
2009	1085	170	28	5	2	0
2010	1200	205	29	5	5	0