Published in final edited form as:

J Allergy Clin Immunol Pract. 2016 ; 4(6): 1182–1186.e1. doi:10.1016/j.jaip.2016.05.006.

EPINEPHRINE AUTOINJECTOR PRESCRIBING TRENDS: AN OUTPATIENT POPULATION-BASED STUDY IN OLMSTED COUNTY, MINNESOTA

Sangil Lee, MD, MS,

Clinical instructor, Department of emergency medicine, Mayo Clinic Health System

Erik P Hess, MD, MSc,

Associate professor, Department of emergency medicine, Mayo Clinic

Christine Lohse, MS,

Department of emergency medicine, Mayo Clinic

Dante Lucas S Souza, and

Department of emergency medicine, Mayo Clinic

Ronna L Campbell, MD, PhD

Assistant professor, Department of emergency medicine, Mayo Clinic

Abstract

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 auto-injectors in Olmsted County, MN residents.

Methods—Outpatient prescriptions for epinephrine were identified among residents of Olmsted County, Minnesota, 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 auto-injector prescriptions during the study period was 757 per 100,000 person-years (95% CI 740–774). The prescription rates per patient per year increased over time, with an annual rate of increase of 8% ($p < 0.001$), but the rates per patient remained stable ($p = 0.077$). For each year, incidence rates overall were higher in women compared

Corresponding author: Sangil Lee, MD, lee.sangil@mayo.edu, Phone: 507-385-2610, Address: 1453 Marsh Street, Mankato, MN 56001.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

to men ($p<0.001$). From ages 0–19, incidence rates were higher in boys compared to girls. At age 20 and above, incidence rates were higher in women compared to men.

Conclusion—The overall rate of epinephrine auto-injector prescriptions increased, but the rate of first time prescriptions was stable from 2005–2010. In childhood, boys were more likely to receive a prescription than girls, but this reversed in later ages.

Keywords

Anaphylaxis; epinephrine auto-injector; epidemiology; incidence rate

INTRODUCTION

Epinephrine auto-injectors are the first line therapy for anaphylaxis and can be administered by laypeople or healthcare providers for the emergency management of anaphylaxis.^{1, 2} Since epinephrine auto-injectors are primarily prescribed to treat or prevent anaphylaxis and related allergic reactions, the prescription trends over time can be used as an indicator of the overall prevalence of patients who have experienced or are at risk of experiencing anaphylaxis.³

Trends of epinephrine auto-injector prescriptions in the United States, however, are not well known.⁴ The Rochester Epidemiology Project (REP) is a record linkage system that connects and indexes the records of virtually all providers of medical care in Olmsted County, Minnesota.^{4–7} Prescription data have become available as a part of the REP since 2003.⁸ Thus, evaluating trends of prescribing for epinephrine auto-injectors 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, Minnesota.

In this study, we used the REP research infrastructure to determine the trends of epinephrine auto-injector 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, MN.

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.⁹ The prescription data captures above 80–90 percent from Mayo Clinic and Olmsted Medical Center, two large healthcare organizations in Olmsted County. A previous study suggested that some non-critical medications may be under-counting but still accurately describe trends.⁸ St. Sauver et al. reported that age, sex, and ethnic characteristics of Olmsted County were similar to those of the state of Minnesota and the Upper Midwest, however, Olmsted County was less ethnically diverse than the entire US population, more highly educated, and

wealthier.⁹ Additional details of REP studies have been published elsewhere.^{9–12} 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 MN. These two institutions provide nearly all of the health care for Olmsted County residents.^{9, 10, 12, 13} Both institutions use electronic prescription systems in outpatient settings. Epinephrine auto-injectors were available in twenty-nine 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, then described first prescription per patient during the study period. Trends for first time prescriptions were analyzed from 2004–2010 to allow for a one year wash out 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 wash out 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 Rochester Epidemiology Project.¹⁴ 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 two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

Overall findings

A total of 7991 prescriptions among 3801 patients from 2004–2010 were identified in Olmsted County. The mean age at the first prescription per year was 31.5 years [median 30 years; interquartile range (IQR) 11–50; range 0–97]. Table 1 shows the number of prescriptions each year and the demographics of the patients who received the prescriptions. The greatest number of prescriptions was written for persons age 0–9 years, followed by 10–19 years. Appendix Table shows the number of prescriptions per patient for each year. Seven

hundred twenty-five patients had one prescription in 2004; 80 patients had two prescriptions although only the first one was analyzed. There does appear to be an increase in the proportion of patients with more than one prescription during the course of a year ($p<0.001$). In 2004, 11% of the patients had more than one 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% 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 2 and shown in Figure 1. Incidence rates differed by age group ($p<0.001$) and by sex ($p<0.001$), and increased over time ($p<0.001$). The highest prescription rate was among boys aged 0–9 years. Prescription incidence rates were higher in boys aged 0–19 years compared to girls; however after age 19, incidence rates were higher in women compared to men.

Incidence rates by year are summarized in Table 3 and shown in Figure 2, and incidence rates of first time prescriptions during the study period in Figure 3, 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 2004–2010 ($p<0.001$). There was no evidence of a statistically significant difference in the rates of increase between different age groups ($p=0.17$). First time prescription rate decreased during 2004–2010 ($p<0.001$), otherwise relatively stable ($p=0.077$) from 2005–2010, yet there was evidence that incidence rates differed by age group ($p<0.001$), differed by sex ($p<0.001$) (Figure 3, 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, Minnesota 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 age 0–19 years compared to 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.

Strengths and limitations

The primary strength of our study is the ability to obtain a population-based estimate of epinephrine auto-injector prescriptions over a 7-year period. Through the Rochester Epidemiology Project collaborations within Olmsted County, we were able to identify above 80–90 percent of all the prescriptions from Mayo Clinic and Olmsted Medical Center, two

large healthcare 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; however we were unable to estimate the use of epinephrine autoinjector in the inpatient setting. Furthermore, we were unable to determine the type of provider who provided the prescription such as an allergist/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 does not include dispensing or insurance coverage information. Sixth, the prescription data does 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 auto-injector prescriptions in the United States over time. For each year of the study period, rates of epinephrine auto-injector prescriptions were higher in women overall compared to men. The highest rates were observed among patients age 0–9 years during which boys received more 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. who studied the population of Manitoba, Canada from 1995–2000.³ Our demographic findings for epinephrine auto-injectors are also consistent with the demographics observed in prior epidemiological studies of anaphylaxis.^{4, 15–17} Overall, we found that epinephrine auto-injector prescription rates were higher in women, which is consistent with findings by Decker et al. who reported that overall rates of anaphylaxis were higher in women than in men.⁴ Mulla et al. reported a finding of higher hospitalization among women than men with anaphylaxis in Florida.¹⁶ Our study showed a higher rate of epinephrine auto-injectors prescriptions for boys age 0–9 compared to girls and higher rates in women over age 20 compared to men. Similar trends have been demonstrated in studies of anaphylaxis-related hospitalizations.^{15–17} Another study from Australia demonstrated that more boys were hospitalized than girls for angioedema, urticaria and anaphylaxis, but this reversed in older ages.¹⁷ A higher rate of anaphylaxis hospitalization for males under 20 years of age was also reported in the US.¹⁵

Incidence rates of prescription were adjusted for population counts by definition. Taken together, the consistency of our findings with extant literature suggests that epinephrine auto-injectors can be used to estimate of the burden of anaphylaxis in a population.⁴¹⁸¹⁹

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 auto-injector prescriptions from 1998–2002.²⁰ A study from Israel also showed that epinephrine auto-injector prescriptions increased by 76% from 1997 to 2004.²¹ Similarly, national healthcare data from the United Kingdom showed a 97% increase in epinephrine auto-injector prescriptions along with increased diagnoses of anaphylaxis between 2001 and 2005.²² These studies reported the crude rate of prescriptions. Thus, our data are consistent with worldwide trends showing increasing rates of epinephrine auto-injector prescriptions, which reflects the increasing prevalence of anaphylaxis. The findings of relatively constant trend for first- time prescriptions during the study period suggests that providers are providing refills of epinephrine prescriptions although it is unknown whether newly diagnosed cases of anaphylaxis patients are receiving necessary prescriptions.

CONCLUSION AND FUTURE DIRECTIONS

Outpatient prescriptions of epinephrine auto-injectors showed an overall increase in all age groups from 2004–2010 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 healthcare providers. Further studies are needed to clearly determine if these trends continue and the appropriateness of epinephrine auto-injector prescribing patterns.

Acknowledgments

We appreciate the valuable input from Hirohito Kita, MD, PhD, James Li, MD, PhD and Amy Weaver MPH at the Mayo Graduate School. This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676, and by CTSA Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Abbreviations

REP	Rochester Epidemiology Project
IQRs	interquartile ranges
CI	Confidence interval
ED	Emergency department

References

1. Campbell RL, Luke A, Weaver AL, St Sauver JL, Bergstralh EJ, Li JT, et al. Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. *Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology*. 2008; 101:631–6.
2. Campbell RL, Manivannan V, Hartz MF, Sadosty AT. Epinephrine auto-injector pandemic. *Pediatric emergency care*. 2012; 28:938–42. [PubMed: 22940899]
3. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *The Journal of allergy and clinical immunology*. 2002; 110:647–51. [PubMed: 12373275]
4. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *The Journal of allergy and clinical immunology*. 2008; 122:1161–5. [PubMed: 18992928]
5. Kurland LT, Molgaard CA. The patient record in epidemiology. *Scientific American*. 1981; 245:54–63. [PubMed: 7027437]
6. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clinic proceedings*. 1996; 71:266–74. [PubMed: 8594285]
7. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: A population-based study. *The Journal of allergy and clinical immunology*. 1999; 104:452–6. [PubMed: 10452770]
8. Zhong W, Maradit-Kremers H, St Sauver JL, Yawn BP, Ebbert JO, Roger VL, et al. Age and sex patterns of drug prescribing in a defined American population. *Mayo Clinic proceedings*. 2013; 88:697–707. [PubMed: 23790544]
9. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clinic proceedings*. 2012; 87:151–60. [PubMed: 22305027]
10. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clinic proceedings*. 2012; 87:1202–13. [PubMed: 23199802]
11. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Pankratz JJ, Brue SM, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *International journal of epidemiology*. 2012; 41:1614–24. [PubMed: 23159830]
12. Rule AD, Jacobson DJ, St Sauver JL, Jacobsen SJ. Re: Ultrasound estimated bladder weight and measurement of bladder wall thickness-useful noninvasive methods for assessing the lower urinary tract? E. Bright, M. Oelke, A. Tubaro and P. Abrams *J Urol* 2010;184:1847–1854. *The Journal of urology*. 2011; 185:2435. author reply. [PubMed: 21513957]
13. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ, Rocca WA. Generalizability of Epidemiological Findings and Public Health Decisions: An Illustration From the Rochester Epidemiology Project. *Mayo Clinic proceedings*. 2012; 87:151–60. [PubMed: 22305027]
14. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *American journal of epidemiology*. 2011; 173:1059–68. [PubMed: 21430193]
15. Lin RY, Anderson AS, Shah SN, Nuruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006. *Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology*. 2008; 101:387–93.
16. Mulla ZD, Simon MR. Hospitalizations for anaphylaxis in Florida: epidemiologic analysis of a population-based dataset. *International archives of allergy and immunology*. 2007; 144:128–36. [PubMed: 17536221]
17. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *The Journal of allergy and clinical immunology*. 2007; 120:878–84. [PubMed: 17931562]

18. Jackson KDHL, Akinbami LJ. Trends in allergic conditions among children: United States 1997–2011. NCHS Data Brief. 2013; 121:1–8.
19. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. The Journal of allergy and clinical immunology. 2014; 133:291–307. quiz 8. [PubMed: 24388012]
20. Kemp AS. EpiPen epidemic: suggestions for rational prescribing in childhood food allergy. Journal of paediatrics and child health. 2003; 39:372–5. [PubMed: 12887669]
21. Levy Y, Segal N, Danon YL. Trends in adrenaline (EpiPen) dispensing in Israel in 1997–2004. Public health. 2007; 121:144–7. [PubMed: 17161854]
22. Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. Journal of the Royal Society of Medicine. 2008; 101:139–43. [PubMed: 18344471]

Highlights Box

1. What is already known about this topic?

The prescription trend of epinephrine auto-injector can be an indicator of the prevalence of patients who have experienced or are at risk of anaphylaxis.

2. What does this article add to our knowledge?

The incidence rate of epinephrine auto-injector prescriptions increased from 2004–2010. In childhood, boys were more likely to receive a prescription than girls, but this reversed in later ages.

3. How does this study impact current management guidelines

Rates of increased epinephrine auto-injector 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 healthcare providers.

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

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

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

Table 1

Summary and demographic characteristics of patients receiving epinephrine auto-injector prescriptions in Olmsted County, MN from January 1, 2004 to December 31, 2010. (N=7991)

Feature	N (%)
Age in years	
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 2

Rates of epinephrine auto-injector prescriptions by age.

Age in years	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.

Table 3

Epinephrine auto-injector prescription rates by year

Year	Women			Men			Both		
	N	Rate [*]	N	Rate [*]	N	Rate [*]	N	Rate [†]	N
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.

Appendix Table

Number of prescriptions per patient, from 2004 to 2010

Year	Number 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