

# Effect of allergen immunotherapy practice parameters on cat extract prescribing patterns, 1993–2009

Brian D. Robertson, MD\*; Robert L. McCoy, BS\*; Michael R. Nelson, MD, PhD\*; and Bret R. Haymore, MD\*

**Background:** Cat extract allergen immunotherapy (AIT) is an effective treatment for cat allergy. The prescribed dose for cat AIT varies among prescribers, despite published data supporting an effective dose range. The original practice parameter published in December 1996 did not recommend a dose of cat allergen, but updates in January 2003 and September 2007 recommend cat extract dose ranges of 2,000 to 3,000 BAU and 1,000 to 4,000 BAU, respectively.

**Objective:** To describe the prescribing patterns for cat AIT among practicing allergists in a large health care system and the effect of practice parameters on these patterns.

**Methods:** A total of 27,788 prescriptions were analyzed to determine the date and amount of maintenance dose cat allergen prescribed. The data were subdivided into periods before and after the 3 published AIT practice parameters.

**Results:** From January 2003 to September 2007, 1,810 prescriptions (18.0%) were written in the recommended range. From September 2007 to May 2009, 3,143 prescriptions (82.6%) were written in the recommended range. Cat AIT maintenance doses were 1,000 to 4,000 BAU 22.1% of the time before January 2003, 61.8% from January 2003 to September 2007, and 82.6% from September 2007 to May 2009.

**Conclusions:** In this large systemic evaluation of cat AIT prescribing patterns, maintenance dose recommendations in the AIT practice parameters were associated with changes in the prescribing patterns for cat AIT. Most prescriptions for cat AIT were inconsistent with recommended doses in the AIT practice parameters between 2003 and 2007. Dosing within recommended ranges improved after 2007, in part due to a widening of the recommended dose range.

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## INTRODUCTION

Allergen immunotherapy (AIT) is an effective treatment for allergic rhinitis and bronchial asthma<sup>1-4</sup> and has been shown to be effective for the treatment of cat dander allergy.<sup>2-8</sup> There is little data in the literature regarding prescribing patterns for cat AIT. A report by Nelson<sup>1</sup> in 2000 demonstrated wide variation in the volume of cat extract included in AIT prescriptions. In that study 71 allergists prescribed cat AIT in doses ranging from 20 to 3,000 BAU, with the median dose of 400 BAU. There has been no large systematic evaluation of cat AIT prescribing patterns reported in the literature since the AIT practice parameters provided a recommended maintenance dose.

The AIT practice parameters from the Joint Task Force on Practice Parameters for cat AIT have evolved with allergen extract standardization and emerging evidence on minimum

effective doses.<sup>9-11</sup> The original AIT practice parameter published in December 1996 gave no recommended dose of cat allergen.<sup>9</sup> In January 2003, the updated practice parameter recommended a maintenance dose of 2,000 to 3,000 BAU (11–17  $\mu$ g of Fel d 1).<sup>10</sup> In September 2007, the practice parameter expanded this recommendation to a maintenance dose of 1,000 to 4,000 BAU (6–23  $\mu$ g of Fel d 1).<sup>11</sup>

The objective of our study was to identify the prescribing patterns for cat AIT among practicing allergists in a large health care system and the effect of AIT practice parameters on these patterns.

## METHODS

The US Army Centralized Allergen Extract Laboratory (USACAEL) provides immunotherapy prescriptions for more than 300 US Department of Defense, US Department of Veterans Affairs, and US Public Health Service clinics. Approximately 20,000 prescriptions are filled each year via an electronic prescribing system, the Extract Lab Management System (ELMS).

Cat AIT prescription data were available in ELMS from July 1993 to May 2009. The data were divided into periods before and after the publication dates of the 3 published AIT practice parameters (December 1996, January 2003, and September 2007).<sup>9-11</sup> Prescribers using the ELMS had the option to put 0 to 10 mL of the stock cat extract in each 10-mL

**Affiliations:** \* Walter Reed Army Medical Center, Washington, DC.

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maintenance (1:1 vol/vol) vial throughout the study period. Prescriptions containing multiple allergens were not excluded from the study. Refill prescriptions were excluded from the analysis. The prescriptions were divided into 10 deciles based on the amount of cat dander extract in the 10-mL vial. The stock cat extract concentration used by USACAEL throughout the study period was the standardized 10,000 BAU/mL of Fel d 1 extract. Maintenance extract vials are 10 mL, and maintenance injection volumes given to patients in this health care system are almost always 0.5 mL. Thus, a prescription for 1 mL of cat extract in a 10-mL maintenance vial would result in a maintenance dose of 500 BAU. The average maintenance dose of cat AIT was calculated for each period demarcated by the AIT practice parameter publications. This study was conducted under an approved institutional review board protocol. The data were deidentified, and no informed consent was required.

## RESULTS

We identified 27,788 new cat AIT prescriptions in the ELMS database containing cat extract from July 1993 to May 2009. A total of 1,539 prescriptions were written from July 1993 to December 1996, 12,237 prescriptions were written from January 1997 to January 2003, 10,072 prescriptions were written from February 2003 to September 2007, and 3,804 prescriptions were written from October 2007 to May 2009. Prescriptions were entered by 394 allergists throughout the study period.

There is a marked increase over time in the percentage of prescriptions within the known effective range of 1,000 to 4,000 BAU. A total of 60% of prescriptions before the September 2007 AIT practice parameters were less than the currently recommended minimum maintenance dose of 1,000 BAU (Fig 1), whereas only 17% of all prescriptions written from October 2007 to May 2009 were less than 1,000 BAU

(Table 1). Only 21% of the prescriptions from July 1993 to November 1996 were within the 1,000- to 4,000-BAU range, whereas 83% of the prescriptions written were within this range from October 2007 to May 2009 (Table 1). Prescriptions above and below this range also decreased over time. Prescriptions less than 1,000 BAU decreased from 71% to 17% from July 1993 to November 1996 and October 2007 to May 2009, and prescriptions greater than 4,000 BAU decreased from 8% to 0.05% between these periods (Table 1). Prescriptions that provided a maintenance dose of 1,000 to 4,000 BAU (the 2007 recommended dose range) occurred 22% of the time before January 2003, 62% from January 2003 to September 2007, and 83% from September 2007 to May 2009.

A total of 280 prescriptions were written for 8 to 10 mL of cat extract in the maintenance vials, which would result in a 4,000 to 5,000 BAU of Fel d 1 maintenance dose for these patients. These prescriptions were almost all (267 of 280) written before 2003. These prescriptions were written by 43 different prescribers, and most of these prescriptions had refills attached to them, which would indicate that the AIT had continued for some time for those patients. No other information, including safety data, was available regarding these patients or the prescribers.

## DISCUSSION

During the 17-year period we studied, the mean volume of cat allergen extract included in new cat AIT prescriptions increased slightly, but wide variability in cat allergen dosing persisted. Evolving specific dosing recommendations in the AIT practice parameters and the studies that those recommendations were based on appear to have influenced allergist prescribing patterns. Most of the cat allergen-containing AIT prescriptions studied were not consistent with the guidelines in the AIT practice parameters between 2003 and 2007. We also noted that maintenance AIT doses for cat extract were less than 1,000 BAU for most prescriptions from July 1993 to January 2003 and that this did not change with publishing of the 1996 practice parameters that did not contain a dose recommendation. However, there was a significant decrease in the number of prescriptions with less than 1,000 BAU after publishing of the 2003 practice parameters, which contained a recommended dose for the first time. Consistency with practice parameter dosing recommendations since 2003 significantly improved after 2007. The progressive increase in cat allergen dose and consistency with minimal effective dose ranges are most likely explained by the emergence of clear dosing recommendations in successive AIT practice parameters.

Our findings suggest that, in the absence of evidence from the medical literature or clear dosing recommendations, most prescribers chose relatively low doses of allergen extract when prescribing cat immunotherapy. However, 2% of prescriptions from 1993 to 2003 used 5,000 BAU for maintenance immunotherapy. This practice virtually ended after the 2003 AIT practice parameters were published, in which spe-

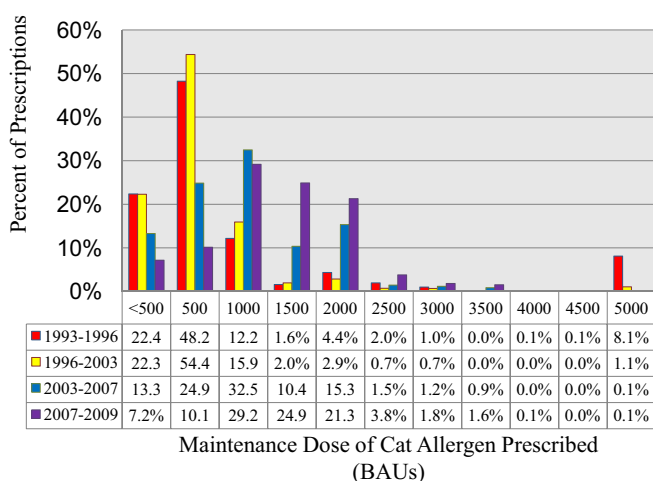


Figure 1. Maintenance dose cat allergen volume for prescriptions (BAU) for each of the 4 periods before and after the 3 allergen immunotherapy practice parameter publication dates.

Table 1. Percentages of Prescriptions Below, Within, and Above the Cat Allergen Maintenance Dose Recommended Ranges for the 2003 and 2007 Practice Parameters<sup>a</sup>

| Maintenance dose volume, BAU              | July 1993 to November 1996 (no BAU recommendation), no. (%) | December 1996 to January 2003 (no BAU recommendation), no. (%) | January 2003 to September 2007 (2,000–3,000 BAU recommended), no. (%) | September 2007 to May 2009 (1,000–4,000 BAU recommended), no. (%) |
|-------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------|
| <2,000                                    | 1,414 (84.42)                                               | 11,574 (94.58)                                                 | 8,159 (81.01)                                                         | 2,716 (71.40)                                                     |
| 2,000–3,000 (2003 recommended dose range) | 123 (7.34)                                                  | 526 (4.30)                                                     | 1,810 (17.97)                                                         | 1,025 (26.95)                                                     |
| >3000                                     | 138 (8.24)                                                  | 137 (1.12)                                                     | 103 (1.02)                                                            | 63 (1.66)                                                         |
| <1,000                                    | 1,183 (70.63)                                               | 9,381 (76.66)                                                  | 3,843 (38.16)                                                         | 659 (17.32)                                                       |
| 1,000–4,000 (2007 recommended dose range) | 355 (21.19)                                                 | 2,725 (22.27)                                                  | 6,219 (61.75)                                                         | 3,143 (82.62)                                                     |
| >4,000                                    | 137 (8.18)                                                  | 131 (1.07)                                                     | 10 (0.10)                                                             | 2 (0.05)                                                          |

<sup>a</sup> Data are divided into periods before and after the 3 allergen immunotherapy practice parameter publication dates.

cific dosing for cat AIT was recommended. These prescriptions were prescribed to individual patients, but it is possible that some were used for diagnostic tests. Our database, unfortunately, does not have a way to track the outcomes and adverse events for these patients. Another limitation of our study is that the actual maintenance dose administered to each patient is not known. For the purposes of this study, it was assumed that 0.5 mL of the 1:1 (vol/vol) maintenance vial was the maintenance dose, which is the usual practice in this medical system.

In 1988 and 1989, van Metre et al<sup>4,5</sup> reported significant improvement in bronchial provocation tests and decreased skin sensitivity to cat extract after cat AIT. Decreased bronchial responsiveness was noted in other studies during the same period.<sup>3,12-14</sup> The Fel d 1 dose given during these trials ranged from 4.3  $\mu$ g to 21  $\mu$ g. Some of the studies used a depot extract, a practice not commonly used in the United States today, making it difficult to compare the dosages given at different points in time.<sup>3,12-14</sup> In 1996, the first set of practice parameters from the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology were released, but no specific dose was recommended for cat AIT.<sup>9</sup>

In 1997, a double-blind, placebo-controlled trial demonstrated rapid improvement in clinical symptoms and on conjunctival challenge to cat extract after treatment with 15  $\mu$ g of Fel d 1 for 3 months.<sup>2</sup> The AIT practice parameter published in 2003 gave the first recommended dose range for cat AIT.<sup>10</sup> On the basis of the above-mentioned study in particular, a maintenance dose of 11 to 17  $\mu$ g of Fel d 1 (or 2,000–3,000 BAU) was recommended for cat AIT.

In 2003, a double-blind, placebo-controlled trial comparing the efficacy of 3 doses of cat AIT showed that a 3.0- or 15.0- $\mu$ g dose of Fel d 1 had decreased skin prick test sensitivity and increased cat specific IgG4 compared with placebo and a 0.6- $\mu$ g dose.<sup>7</sup> The AIT practice parameter published in 2007 increased the recommended dose range to 1,000 to

4,000 BAU (6–23  $\mu$ g of Fel d 1).<sup>11</sup> This widening of the recommended dose range was based on the findings from this study and is supported by findings from previous studies that demonstrated optimal cat AIT efficacy and safety within this dose range.<sup>2,4-6,8</sup>

Alternatives to subcutaneous AIT for cat allergens are currently being investigated. Preliminary studies have been performed with sublingual immunotherapy (SLIT) for cat allergy. Alvarez-Cuesta et al<sup>15</sup> demonstrated a reduction in peak expiratory flow response and symptoms during a natural challenge test to cat allergen after 1 year of treatment with cat extract SLIT. Phase 1 trials of cat allergen SLIT have been completed in the United States, and efficacy studies are currently under way.<sup>16</sup> Cat allergen SLIT remains investigational in Europe and the United States, and an optimal dose as not yet been determined.<sup>17-19</sup> Hypoallergenic Fel d 1 peptides, created by disrupting Fel d 1 B-cell epitopes while keeping T-cell epitopes intact, are currently being developed.<sup>17</sup> Synthetic T-cell epitope-containing peptides have been studied but have had mixed safety and efficacy results.<sup>20</sup> It is, however, difficult to assess the effect of published studies and guidelines, such as the 2009 World Allergy Organization position paper on prescribing practices, for these evolving new therapies on the prescribing practices for subcutaneous AIT.

Our data suggest that the presence of a specific maintenance dose recommendation in the AIT practice parameters and the research supporting the recommendation may contribute changes in cat allergen prescribing patterns. This finding highlights the importance of clear guidelines and evidence-based medicine in providing guidance as to the optimal dose of cat AIT that is efficacious and safe. To our knowledge, this is the first large published systematic evaluation of cat AIT prescribing patterns since the practice parameters provided a dosing recommendation. Future studies should evaluate the safety of different doses and build-up

schedules along with how individual prescribing patterns may change over time.

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Reprint requests should be addressed to:  
 Brian D. Robertson, MD  
 Department of Allergy/Immunology  
 Walter Reed Army Medical Center  
 6900 Georgia Ave NW  
 Washington, DC 20307  
 E-mail: [brian.robertson@amedd.army.mil](mailto:brian.robertson@amedd.army.mil)