Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis

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Background: Venom immunotherapy (VIT) is a treatment with established efficacy for the prevention of repeated anaphylactic reactions in patients with Hymenoptera allergy, which also allows patients to discontinue carrying an EpiPen. Despite their merits, both treatments can have negative aspects potentially important to patients.
Objective: We examined possible negative aspects of the EpiPen in comparison with VIT as perceived by patients.
Methods: Positive and negative aspects of both treatments were measured by using a burden of treatment questionnaire together with statements about the EpiPen.
Results: One hundred ninety-three patients were included, of whom 94 consented to randomization: 47 received VIT, and 47 received the EpiPen. Of the remaining 99, 75 chose VIT, and 26 chose the EpiPen. Of the patients receiving VIT, 91.5% were (extremely) positive about their treatment, and 85% would choose VIT again. Of the patients receiving the EpiPen, only 48% were positive about their treatment, and even of these patients, 68% preferred to be treated with VIT after 1 year of carrying the EpiPen. Although most patients indicated that it is reassuring to carry an EpiPen and makes them feel safe, many patients also indicated that it is inconvenient and troublesome. Especially patients who were negative about the EpiPen indicated that they would not dare use the EpiPen if necessary and were afraid at possible side effects.
Conclusion: In contrast to VIT, the EpiPen is perceived as burdensome by most patients with venom allergy. For most patients, an EpiPen is an unsuitable definitive treatment.
Clinical implications: As VIT enables patients with venom allergy to get rid of the EpiPen, patients should be offered VIT.
(J Allergy Clin Immunol 2006;118:699-704.)

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Supported by ALK-Abelló, Denmark.
Disclosure of potential conflict of interest: J. N. G. Oude Elberink has received grant support from HAL Allergy. A. E. J. Dubois has consultant arrangements with ALK-Abelló and has received grant support from ALK-Abelló, Diagnostic Products Corp, and Pharmacia. The rest of the authors have declared that they have no conflict of interest.
Received for publication April 2, 2005; revised February 24, 2006; accepted for publication March 17, 2006.
Available online July 25, 2006.

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0091-6749/$32.00

doi:10.1016/j.jaci.2006.03.049

Key words: *EpiPen, quality of life, yellow jacket allergy, venom immunotherapy, insect allergy, venom allergy, burden of treatment*

Patients with insect venom allergy are routinely advised to carry an EpiPen (ALK-Abelló, Nieuwegein, The Netherlands) as either temporary or, in some cases, definitive treatment for their allergy. In contrast to most other forms of anaphylactic allergy, patients with insect venom allergy can also be treated with venom immunotherapy (VIT),[1] which generally enables patients to discontinue carrying the EpiPen.

Patients with insect venom allergy experience several problems concerning their health-related quality of life (HRQL),[2] and carrying an EpiPen as sole treatment is not able to ameliorate or even prevent deterioration of quality of life.[2] In contrast, VIT improves HRQL.[3] However, recommendations concerning the use of VIT are not the same in all parts of the world. In the United States VIT is recommended for all adult patients who have experienced systemic reactions after an insect sting.[4] In many European centers VIT is only recommended for more life-threatening reactions,[5] and patients with less serious reactions are often offered an EpiPen as sole treatment, sometimes for life. Reasons for withholding VIT (and giving only an EpiPen) include concerns regarding safety and the notions that VIT is uncomfortable, burdensome to the patient, and ultimately unnecessary.

However, carrying an EpiPen might also cause problems for patients. In most patients the compliance is low, and the ability to correctly self-administer it is poor.[6] Despite their merits, both treatments can have negative aspects important to patients.

We examined the possible negative aspects of VIT, as well as those of the EpiPen, as perceived by patients by using a burden of treatment (BoT) measurement. We asked patients who had experienced both therapies to compare the EpiPen and VIT and to indicate which treatment they would have preferred if they could choose either treatment again. We also included statements about the EpiPen to examine negative and positive aspects of carrying this emergency medication.

METHODS

Patients

Patients were recruited from the allergy outpatient department. Consenting patients aged 18 to 65 years were included if they had

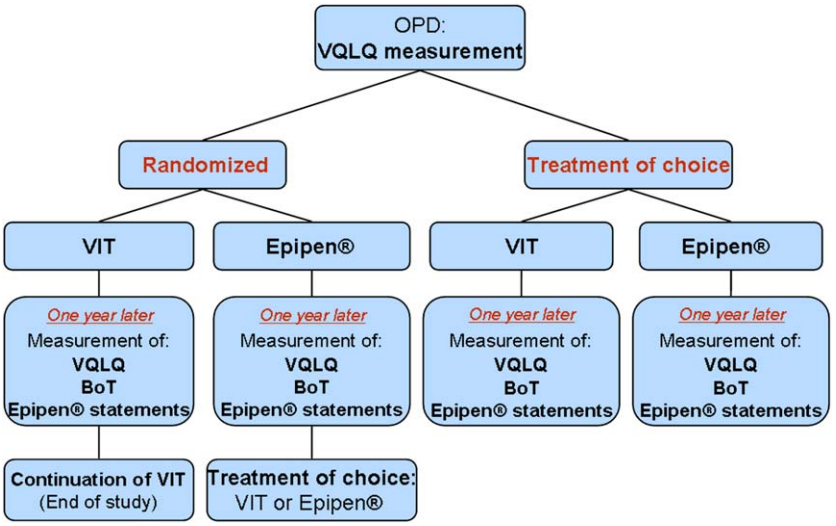

FIG 1. Flow chart of the study. Measures include VQLQ, BoT, and EpiPen statements.

Abbreviations used
BoT: Burden of treatment
HRQL: Health-related quality of life
STAI: State-Trait Anxiety Inventory
VIT: Venom immunotherapy
VQLQ: Vespid Allergy Quality of Life Questionnaire

experienced one or more anaphylactic reactions after yellow jacket stings and were sensitized to yellow jacket venom.

Study design

All patients with a suspected systemic reaction after an insect sting and visiting our outpatient clinic were prescribed an EpiPen if they did not already have one. All received both extensive instruction and written information about how and when to use the EpiPen immediately after referral and before physician contact. Briefly, patients were instructed to have an EpiPen available at all times. After an insect sting, patients were instructed to make the EpiPen ready for use and to wait to see whether a reaction developed. They were instructed to use the EpiPen if they felt throat tightness, dyspnea and/or chest tightness, and/or lightheadedness. They were also told to err on the side of safety and use the EpiPen if they had serious concerns about the impending reaction. Finally, they were instructed to seek definitive medical treatment immediately after using the EpiPen.

All patients received information about the study and received the same standardized information about risks and benefits of the EpiPen and VIT in a "patient information document."[3] In this document patients were informed that the chance of a more severe reaction than the previous reaction they had experienced was low but that such reactions are possible. This information was also explained by a trial technician who was trained to present and explain the document in an objective and uniform manner, without expressing a preference for either treatment. Patients were asked whether they were willing to participate in the study. If they consented to randomization, they were allocated to one of the 2 open-label study arms, namely VIT for 1 year or carrying an EpiPen for the same time period. If patients refused randomization, they were asked to participate in a nonrandomized longitudinal study with their preferred treatment, either VIT or the EpiPen.

As previously described,[3] all patients were evaluated on 2 occasions (Fig 1). During the first visit, patients were given a set of measures, including the Vespid Allergy Quality of Life Questionnaire (VQLQ) and the Dutch adaptation of the Spielberger State-Trait Anxiety Inventory (STAI), from which the trait anxiety was used (the STAI version DY-2).[7] For a further exploratory analysis, a BoT question and statements about the EpiPen were also included.

After 1 year of treatment with either VIT or an EpiPen, the set of measures were readministered. The randomized study then ended. Patients randomized to the EpiPen were asked whether they preferred to continue to carry their EpiPen or whether they wished to start VIT.

Patients randomized to or choosing the EpiPen carried their EpiPen for at least 1 year without receiving VIT. Patients who started VIT carried an EpiPen until reaching the maintenance dose. Thus the time during which the EpiPen was carried varied from weeks to years because some patients were referred to our clinic years after experiencing an anaphylactic reaction.

All patients participating in the study provided their written informed consent. The study was approved by the Medical Ethics Committee of University Hospital Groningen. Patients had to pay for their EpiPen during the study. Patients did not pay for their venom extracts (all patients had health insurance, which covered VIT but not the EpiPen during the period this study was carried out). They were not compensated for travel or other expenses.

Statements about the EpiPen

Statements were generated by means of focus groups and clinical experience of the investigators. Patients were asked what items concerning the EpiPen in their day-to-day life were important to them. The items that were consistently cited by patients were included in the questionnaire. A total of 14 statements were included in the questionnaire about the EpiPen (Table I). Half of the statements were worded positively and half of the statements were worded negatively to compensate for agreement bias. The questions were presented in a random order.

The BoT question

The BoT measurement was carried out after 1 year of treatment with VIT or the EpiPen. Patients were asked to weigh the advantages and disadvantages of their treatment on a 7-point scale, ranging from extremely positive (score 1) to extremely negative (score 7, Table II). After 1 year of treatment with VIT, patients who had thus experienced

TABLE I. Positively worded statements about the EpiPen measured in both EpiPen treatment groups (randomized [n = 46] vs patients choosing this treatment [n = 24])

Which of the following statements concerning the EpiPen is true, in your opinion?	Agree, n (%)*	Disagree, n (%)*	No opinion, n (%)*	Correlation with BoT† (r)	Difference between the 2 treatment groups‡
Positively worded statements					
1. Carrying an EpiPen makes you feel safe.	56 (81.2)	9 (13.0)	4 (5.8)	0.35 ($P = .02$)	NS
2. It is reassuring to carry an EpiPen.	61 (87.0)	5 (7.2)	4 (5.8)	0.32 ($P < .05$)	NS
3. The EpiPen is sufficient for the treatment of an allergic reaction.	30 (43.5)	19 (27.5)	20 (29.0)	0.35 ($P < .05$)	NS
4. The EpiPen can cure your allergy.	1 (1.4)	62 (88.6)	7 (10.0)	NS	NS
5. The EpiPen is worth the cost.	49 (72.1)	4 (5.9)	15 (22.1)	NS	NS
6. The EpiPen is a patient-friendly form of treatment.	48 (70.6)	7 (10.3)	13 (19.1)	NS	NS
7. The EpiPen is patient friendly because of its size.	27 (40.3)	32 (47.8)	8 (11.9)	NS	NS
Negatively worded statements					
8. It is inconvenient to have to carry an EpiPen.	44 (62.9)	26 (37.1)	0	−0.32 ($P < .05$)	$P < .05$
9. It is troublesome to carry an EpiPen.	50 (73.5)	18 (26.5)	0	−0.37 ($P = .02$)	NS
10. I am concerned that a single EpiPen might be insufficient for the treatment of an allergic reaction.	13 (18.6)	42 (60.0)	15 (21.4)	NS	$P = .002$
11. Having to pay for the EpiPen is a problem.	43 (62.3)	18 (26.1)	8 (11.6)	NS	NS
12. The EpiPen is too expensive.	43 (61.4)	8 (11.4)	19 (27.1)	NS	NS
13. I think I would not dare use the EpiPen if this were necessary.	8 (11.6)	56 (81.2)	5 (7.2)	−0.36 ($P = .02$)	NS
14. I am afraid of the side effects of the EpiPen.	15 (21.7)	42 (60.9)	12 (17.4)	−0.39 ($P = .02$)	NS

*The percentages pertain to both treatment groups.
†Correlations with the BoT were measured with the Pearson correlation coefficient.
‡Differences between both treatment groups were measured with the Fisher exact test.

both treatments were asked to indicate which treatment they would have chosen initially.

After 1 year of VIT, patients were asked some additional questions about the EpiPen:

- How do you feel about the fact that you do not need the EpiPen anymore (7-point response scale from extremely positive to extremely negative)?
- Do you still carry the EpiPen, and if so, why (no or yes with open options)?
- What is your overall treatment of choice now that you have experienced both therapies (VIT only, VIT but with EpiPen, EpiPen only, no preference)?

Statistical analysis

The results of the BoT questionnaire were analyzed in both randomized treatment groups (the results of the first 70 patients have been published previously[3]). The score ranges from 1 (extremely positive) to 7 (extremely negative). A score from 1 to 3 was defined as a positive BoT, and a score of 4 to 7 was defined as a negative BoT. Differences in outcome of the BoT and differences in patient characteristics between the different BoT groups were analyzed with the Student *t* test.

The results of the EpiPen statements were analyzed in patients who received the EpiPen as sole treatment (randomized and nonrandomized). Differences between these treatment groups were measured with the Fisher exact test. Differences in patient characteristics between the randomized and nonrandomized patients were analyzed with the Student *t* test.

VQLQ scores ranged from 1 (no impairment) to 7 (severe impairment in quality of life).[3] The STAI anxiety disposition levels range from 1 to 10. A score lower than or equal to 5 was defined as a low anxiety level, and a score higher than 5 was defined as a high anxiety level.

The BoT question was validated in patients from both randomized treatment groups by correlating the BoT with the change in VQLQ score, as measured with the Pearson correlation coefficient. The EpiPen questionnaire was validated in patients randomized to the EpiPen by correlating each EpiPen statement with the positive or negative outcome of the BoT.

The Cronbach reliability coefficient was used to assess the internal consistency of the EpiPen statements that could be validated by means of correlation with the BoT. An α value of greater than .7 was taken as reliable.

TABLE II. BoT question

BoT
1. *Extremely positive*: The treatment* has clear advantages and no important disadvantages.
2. *Positive*: The treatment* has more advantages than disadvantages.
3. *Slightly positive*: The treatment* has somewhat more advantages than disadvantages.
4. *Neutral*: Advantages and disadvantages of the treatment* are equal.
5. *Slightly negative*: The treatment* has somewhat more disadvantages than advantages.
6. *Negative*: The treatment* has more disadvantages than advantages.
7. *Extremely negative*: The treatment* has clear disadvantages and no important advantages.

Patients were asked to weigh the advantages and disadvantages of their treatment* (VIT or the EpiPen) on a 7-point scale.

RESULTS

Patients

A total of 193 patients were included in the study, of whom 94 consented to randomization. In patients receiving VIT, no systemic side effects occurred. Two patients

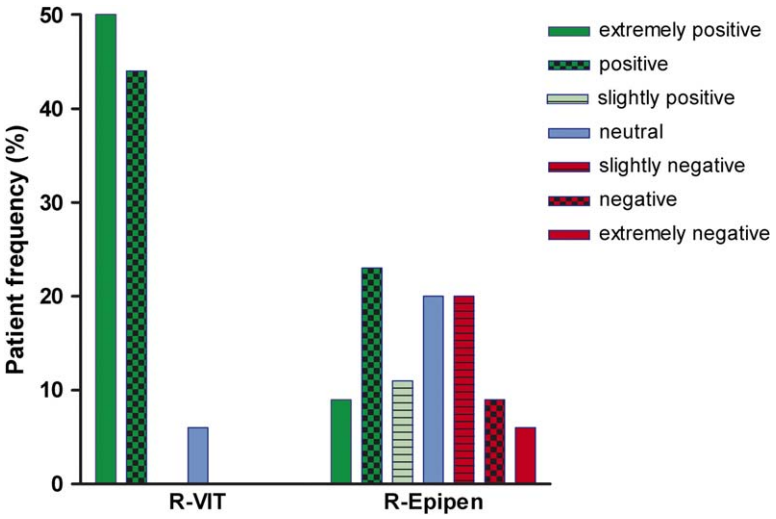

FIG 2. Results of the BoT question for each treatment group. Significantly more patients had a negative opinion about the EpiPen than about VIT. Conversely, significantly more patients had a positive opinion about VIT than about the EpiPen ($P < .001$). *R-VIT,* Patients randomized to VIT; *R-EPI,* patients randomized to the EpiPen.

TABLE III. Choice of treatment after carrying an EpiPen for 1 year as only treatment in relation to the results of the BoT measurement

Randomized EpiPen group (n = 46): results of BoT		
Treatment choice after 1 y of treatment with EpiPen	**Positive overall assessment**	**Neutral/negative overall assessment**
VIT	15	21
EpiPen	7	2
Lost to follow-up	0	1
Total	22	24

experienced a field sting during the study, one in the randomized EpiPen group, resulting in symptoms for which the EpiPen was used, and one in the randomized VIT group with no sequelae. In patients receiving VIT, no systemic side effects occurred. The BoT of all 47 patients randomized to VIT could be analyzed. Of the 47 patients randomized to the EpiPen, 46 could be analyzed. Of the remaining 99 nonrandomized patients, 75 chose VIT, and 24 patients preferred to carry the EpiPen as sole treatment.

The BoT questionnaire

There was an inverse correlation between the change in VQLQ score and the BoT: the greater the improvement in VQLQ score, the more positive patients were about their treatment ($r = -0.42$, $P < .001$), thus validating the BoT instrument.

The results of the BoT in the first 70 patients randomized[3] have been expanded to include a total of 93 patients. Of the 47 patients randomized to VIT, 91.5% were positive to extremely positive about their treatment (Fig 2). None of the patients were negative about this treatment. This is in contrast to the group randomized to the EpiPen, in which 29.5% had negative opinions, including extremely negative opinions in 2 patients and 4 very negative opinion. In this group 47.7% had a positive opinion about the EpiPen, and 10 patients had neutral opinions. However, of patients who chose the EpiPen, 76.9% were positive about their treatment.

There was no correlation between a positive overall assessment of the EpiPen as measured by the BoT and different patient characteristics, including sex, general anxiety, initial quality-of-life score, severity of the reaction, and time since the last reaction, except for age: younger persons were more positive in their opinion about the EpiPen ($r = 0.31$, $P = .04$).

After 1 year of carrying an EpiPen, patients could determine their treatment of choice: 78% preferred to start VIT. Even of the 22 patients who were positive about the EpiPen, 68% preferred to start VIT, and only 7 preferred to continue to carry their EpiPen (Table III). The patients who chose to continue to carry their EpiPen were relatively younger than those choosing VIT (age, 31.8 vs 44.3 years; $P < .05$). Almost all patients who were negative about the EpiPen (87.5%) preferred to start with VIT after carrying an EpiPen for 1 year. Two patients preferred to continue to carry the EpiPen as their only treatment, despite their negative assessment, and 1 was lost to follow-up.

In contrast to the randomized EpiPen patients, almost all patients randomized to VIT were positive about their therapy (Table IV), and 47% were extremely positive. This was especially the case for the patients with a more impaired compared with a less impaired pretreatment VQLQ score (2.63 vs 3.77, $P = .02$). Although the group who was neutral about VIT was very small (n = 3), their change in VQLQ was significantly smaller than the patients positive about VIT (0.28 vs 1.00, $P < .05$). There was a positive correlation between a positive judgment

TABLE IV. Preferred initial treatment after 1 year of treatment with VIT in relation to the results of the BoT

Randomized VIT group (n = 47): results of BoT		
Preferred initial treatment after 1 y of treatment with VIT	**Positive overall assessment**	**Neutral overall assessment**
VIT	40	2
VIT with EpiPen	3	1
EpiPen	0	0
No opinion	1	0
Total	44	3

Patients were asked to indicate which treatment they would have chosen initially after having experienced both treatments.

about VIT and the statement that it is inconvenient to carry an EpiPen ($r = 0.32$, $P < .05$).

Almost all (94.7%) patients randomized to VIT were (extremely) positive that they did not need to carry the EpiPen anymore, although 20% (n = 8) still carried their EpiPen with them. Patients with a lower posttreatment VQLQ score (3.79 vs 4.53, $P < .001$) and women more than men (75% vs 25%, $P = .05$) preferred to continue to carry the EpiPen. Of the 8 patients who still carried the EpiPen, only one third found carrying their EpiPen gratifying. After 1 year of treatment with VIT, the vast majority of the patients (90%) would have chosen VIT again. Only 1 patient would have chosen the EpiPen as the only treatment.

Statements about the EpiPen

Each statement about the EpiPen was correlated with the outcome of the BoT to validate the EpiPen questionnaire. A low BoT score (positive opinion about the EpiPen) correlated with the following statements: ''the EpiPen makes you feel safe'' ($r = 0.30$, $P = .02$), ''carrying an EpiPen is reassuring'' ($r = 0.32$, $P < .05$), and ''the EpiPen is sufficient to treat an allergic reaction'' ($r = 0.35$, $P < .05$). A high BoT score (negative opinion about the EpiPen) correlated with the statements ''it is inconvenient to have to carry an EpiPen'' ($r = -0.32$, $P < .05$), ''it is troublesome to carry an EpiPen'' ($r = -0.37$, $P = .02$), ''I think I would not dare use the EpiPen if necessary'' ($r = -0.36$, $P = .02$), and ''I am afraid of the side effects'' ($r = -0.39$, $P = .02$). None of these questions correlated inversely with the BoT. The other questions did not correlate with the BoT. The Cronbach α value of the positively worded EpiPen statements correlating with the BoT was 0.79, whereas the Cronbach α value of the negatively worded EpiPen statements correlating with the BoT was 0.63.

Statements about the EpiPen were analyzed in patients randomized to the EpiPen and compared with those of patients choosing this treatment. For patients randomized to the EpiPen, it is more often inconvenient to carry an EpiPen than for patients choosing the EpiPen (72.9% vs 46.2%, $P < .05$). None of the patients choosing the EpiPen was concerned whether a single EpiPen might be insufficient in contrast to patients randomized to the EpiPen, where 29.5% agreed with this statement ($P < .01$). Those who were concerned that a single EpiPen might be insufficient were those with a higher anxiety score (37.2 vs 30.2, $P < .05$) and those with a lower pretreatment VQLQ score (3.86 vs. 4.87, $P < .04$). There were no differences found between randomized and nonrandomized groups for all other statements. The results shown in Table I are of both groups together.

In comparison with patients with a positive opinion about the EpiPen, patients with a negative opinion disagree more often with the statement that the EpiPen makes them feel safe (31.6% vs 4.7%, $P < .05$). They agree more often with the statements that it is troublesome (95.5% vs 66.6%, $P < .05$) and inconvenient (87% vs 59.1%, $P < .05$) to carry an EpiPen. They also think more often that they ''would not dare use the EpiPen if this were necessary'' (31.6% vs 4.5%, $P < .05$) and are more often ''afraid of the side effects of the EpiPen'' (43.8% vs 10%, $P < .05$).

For 70.6% of the patients, the EpiPen is a patient-friendly form of treatment. However, in the randomized group younger patients disagreed more often with this statement than the older patients (32.8 vs 44.1 years of age, $P < .04$), and they were all women. Older patients were more afraid of the side effects than the younger patients (48.7 vs 35.3 years of age, $P < .05$).

DISCUSSION

VIT and prescription of an EpiPen are both treatment modalities that might be recommended under different circumstances in patients allergic to Hymenoptera venom. In the absence of a universally recognized medical indication for VIT, such as serious reactions, life-threatening reactions, or both to stings in the past, treatment recommendations with regard to the choice between VIT and an EpiPen are variable and often rationalized by presumed patient preferences and attitudes. We have previously shown that HRQL in patients allergic to insect venom improves when undergoing treatment with VIT, whereas treatment with an EpiPen alone is accompanied by a deterioration in HRQL.[3] Also in this study, 68% of the patients, although they were positive about the EpiPen, still preferred to receive VIT after a year of carrying the EpiPen. The preference for VIT was further established by the fact that after having experienced both treatments, none of the patients randomized to VIT would have chosen the EpiPen initially as sole treatment. Only 3 of 47 indicated that they would like to carry an EpiPen in combination with VIT. Considered together, these results demonstrate the superiority of VIT to EpiPen for most patients. Despite this, it could be argued that these beneficial aspects are outweighed by the negative aspects of VIT and that administration of an EpiPen would still be the preferred treatment for many patients.

Using a BoT question, we compared the negative and positive aspects of the EpiPen and VIT. The validity of this question was established by the correlation between the BoT and the change in VQLQ score, showing that the

more positive patients were about their treatment, the greater the improvement in their VQLQ scores. Almost all patients receiving VIT indicated that not being required to carry an EpiPen was a major benefit of VIT. These findings suggest that the deterioration in HRQL seen in patients treated with an EpiPen might at least in part be due to a negative effect on HRQL of the EpiPen itself. For the clinician, this would imply that optimal HRQL results will usually not be achieved if patients are advised to continue carrying an EpiPen while undergoing treatment with VIT. A trial comparing these 2 treatment options directly would be needed to confirm these findings and determine the magnitude of the negative effect on HRQL caused by the EpiPen.

The EpiPen statements were used to explore the reasons for the negative or positive opinion about the EpiPen. For many statements (statements 4-7 and 10-12), patients had the same opinion, independent of whether they had a positive or negative overall opinion about the EpiPen. For other individual statements, a correlation with the BoT could be demonstrated, providing evidence for the measurement properties of these questions and thus providing a possible explanation why patients have a positive or negative opinion, respectively, about the EpiPen. Interitem variability for negatively worded statements about the EpiPen was greater than for the positively worded statements (Cronbach $\alpha = 0.63$ vs 0.79). This might be due to greater differences between patients in the relative importance of their negative feelings about this treatment than the more rational advantages of this therapy.

By using the BoT, there were no patients undergoing VIT who were negative about this treatment. This is in contrast to almost 30% of the patients receiving an EpiPen as sole treatment who were negative to extremely negative about this treatment. For these patients, carrying an EpiPen was more often inconvenient and troublesome and less often gave them a safe feeling than patients with a positive opinion about the EpiPen. However, even in patients with a positive opinion ($n = 22$) about the EpiPen, many indicated that it is inconvenient (59%) and troublesome (64%) to carry an EpiPen. These feelings of burden probably result in patients not carrying the EpiPen, as has been studied by Goldberg and Confino-Cohen,[6] who found that only a minority of patients carried their EpiPen at all times. In our study we did not study whether patients carried their EpiPen.

In the same study by Goldberg and Confino-Cohen,[6] 23% of patients with insect sting reactions admitted that they probably would not have the courage to self-administer the EpiPen. This is comparable with our data, which showed that 21.7% of patients indicated that they were afraid of potential side effects, and 18% indicated that they would not dare to use the EpiPen. Especially older patients were more afraid of the side effects than younger patients, possibly because the risks of complications, such as cerebral hemorrhage or pulmonary edema, are more relevant for older subjects. Moreover, negative assessments of the EpiPen were more strongly related to negative perceptions of this treatment than to a lack of appreciation of the positive aspects of such treatment. These findings are of importance because it has been suggested that fear of side effects, fear of (self-) administering an injection, or both might contribute significantly to underuse of the EpiPen in patients undergoing anaphylactic reactions.[8] Several studies have shown that such underuse increases the risk of a bad outcome, including an increased risk of death.[9-11] These results suggest that patient education should identify and correct patient fears regarding EpiPen use to increase compliance. New (convincing) techniques are likely to be necessary to achieve this goal, and such methods need to be developed.

In conclusion, these results suggest that in addition to being associated with a deterioration in quality of life,[3] the EpiPen is perceived by many patients as burdensome and is therefore suboptimal monotherapy for most patients with insect venom allergy. Patient education should address negative attitudes concerning the EpiPen in an effort to improve compliance and improve outcomes. Because patients do not perceive VIT as burdensome and it allows patients with insect venom allergy to discontinue carrying an EpiPen, VIT is the treatment of choice for the vast majority, even in patients with less severe systemic reactions after an insect sting.

We thank Ms Henriëtte Beverdam for technical support.

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