

Out-of-season recollection of drug use for seasonal IgE-mediated rhinitis: Useful but an overestimation

Uffe Bodtger, PhD, Hans-Jørgen Malling, MD, and Lars K. Poulsen, PhD *Copenhagen, Denmark*

Background: The history of seasonal, IgE-mediated (allergic) rhinitis is often obtained postseasonally as a retrospective assessment. It is not known whether recollected drug use is representative for the in-seasonal medication history.

Objectives: To investigate the agreement between in-seasonal and out-seasonal reports on drugs and drug doses, and to investigate whether retrospective assessment was sufficiently sensitive to detect the effect of intervention.

Material and methods: Thirty-five patients allergic to birch pollen were allocated to allergen-specific immunotherapy (SIT) or placebo in a double-blind study. Drug use was recorded daily during the season 2000 and out-seasonally 6 months after the seasons 1999 and 2000. The mean daily drug use was transformed into a 4-point categorical scale for simplicity and was calculated for the out-seasonal rating and for 6 in-seasonal periods of different durations. In-seasonal and postseasonal ratings were compared with the Cohen weighted κ (κ_w).

Results: We observed a high level of agreement between in-seasonal and retrospective reports of drugs used ($\kappa_w > 0.60$) and drug doses ($\kappa_w > 0.50$). The highest agreement was observed for the in-seasonal day, week, or 2 weeks with the highest drug intake. Out-seasonal ratings significantly overestimated the daily oral and nasal antihistamine use compared with in-seasonal periods >2 weeks. Despite being comparable pretreatment, only the SIT group had a significant decrease in recollected total drug use during SIT.

Conclusion: Out-seasonal recollection of hay fever drugs represented a period of a maximum 14 days. It appeared sufficiently sensitive to detect the effect of intervention.

(*J Allergy Clin Immunol* 2005;115:786-90.)

Key words: IgE, rhinitis, allergy, retrospective, recollection, immunotherapy, medication, birch

Drug adherence is a main factor when treating any medical disease. Patients' adherence to antiallergic drugs has not been investigated. It is known that patients tend to overestimate the use of inhaled corticosteroids in

Abbreviations used

DD: Daily drug dose

SAR: Seasonal, IgE-mediated (allergic) rhinitis

SIT: Allergen-specific immunotherapy

nonallergic asthma when reporting the consumption during the previous 6 months.¹ Patients treated with antiviral drugs for AIDS also tend to overreport the daily use, especially when retrospectively describing periods longer than 2 weeks.^{2,3} Likewise, we have previously reported that retrospective assessment of symptom severity in seasonal, IgE-mediated (allergic) rhinoconjunctivitis (SAR) correlates best to a period of maximal 14 days, which is much shorter than the allergen season.⁴ Yet retrospective assessment was sufficiently sensitive to detect the effect of intervention (allergen-specific immunotherapy [SIT]). Out-seasonal recollection of severity of SAR is widely used: in daily clinical life when evaluating the indication of SIT,⁵ or when screening patients with SAR before participation in clinical, *in vitro*, or epidemiological studies.⁶⁻⁸ Because antiallergic drugs modulate the objective and subjective severity of SAR, we investigated the agreement of daily drug use reported in in-seasonal (prospectively completed) daily diaries and at an out-seasonal (retrospectively completed) interview.

METHODS

Patients

In a specialized allergy clinic, 35 patients (14 male) age 27 (range, 19-45) years with birch pollen SAR were included in a double-blind, placebo-controlled clinical study on birch pollen SIT. Patient selection and SIT protocol are described in detail in a previous report.⁹ Briefly, all reported SAR in ≥ 2 preceding seasons, had a positive birch pollen skin prick test result (mean wheal diameter ≥ 3 mm, Soluprick; ALK-Abelló, Hørsholm, Denmark), had birch pollen specific serum IgE $\geq$ CAP class 3 (CAP system; Pharmacia, Uppsala, Sweden), and were conjunctival challenge-positive (Aquagen birch; ALK-Abelló). SIT was performed in our institution between January and October 2000 by an experienced staff by using a commercially available high-dose birch pollen extract (Alutard; ALK-Abelló). SIT was administered subcutaneously on the upper arm every week for 8 weeks, and then

From the Allergy Clinic, National University Hospital.

Supported by a grant from the Danish Allergy Research Center, Denmark.

Received for publication October 29, 2004; revised December 16, 2004; accepted for publication January 3, 2005.

Reprint requests: Uffe Bodtger, MD, Allergy Clinic 7551, National University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: ub@dadlnet.dk.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.01.032

every 8 weeks, reaching a cumulative dose of 92 µg of major allergen, *Bet v 1*, at follow-up. SIT and placebo groups were comparable in age, sex, symptom severity at onset, asthma prevalence, and grass SAR prevalence.^{4,9} None had perennial rhinitis or asthma or other diseases requiring anti-inflammatory treatment. The study was approved by the local ethics committee of Copenhagen, Denmark, and written informed consent was obtained from all patients before admission to the study.

Birch pollen season

Birch pollen grains were collected and counted by the Danish Meteorological Institute, Copenhagen,¹⁰ and expressed as number of grains/m³ air. The birch-pollen season (in year 2000, referred to as *season*) was defined as the period covering the mid-90% of the total birch pollen count.⁹ Because symptoms and pollen counts are not parallel,⁹ we defined a *birch symptom period* in 2000 from start of season to another outdoor allergen count exceeding symptom-inducing levels: in Denmark, >10 grass pollen grains/m³.^{10,11}

Reported medication use

At inclusion (autumn 1999) and at follow-up (autumn 2000), patients were interviewed on drug use during the preceding season and reported name (brand or generic), dose (mg or mg/mL), frequency of dispensing (times/d), and duration of treatment (daily or number of days) of each drug used in the preceding season. Recollection was completed in absence of any in-seasonal data and before unblinding the SIT study.⁹

From March 13 to May 25, 2000, all patients completed (at home) daily diary cards on medication use: name (brand or generic), dose (mg or mg/mL), and frequency of dispensing (times/d).

Daily drug use

An in-seasonal mean daily use of each drug (mean DD) was calculated for 6 different periods on the basis of area under the curve: the single day, the single week, and the 2 weeks with the highest mean DD for each patient, the season, the birch symptom period, and the day with the most severe SAR symptoms.⁴

An out-seasonal mean DD was calculated by the product of dose, frequency, and days of use, divided by number of days in the season. The latter served also as rough adjustment for interseasonal differences in allergen exposure.⁴

The mean DD was expressed relatively to the defined daily dose for optimal efficacy.¹²⁻¹⁴ For simplicity, the ratio was transformed into a 4-step categorical variable: 0.00 = drug not used; 0.01 to 0.49 = slight use; 0.50 to 0.99 = moderate use; and ≥1.00 = maximal or extensive use.

Drugs used

Table I shows the drugs used during the season 1999 (only out-seasonally reported) and 2000. We focused on the recollection of drug groups rather than on each drug. Because only 2 patients used chromones (eye drops), this drug was pragmatically fused with ocular antihistamine into 1 group. During the SIT study, we provided the patients with rescue medication (marked with * in Table I). Observe that corticosteroids were deliberately avoided to prevent obscuring the effect of SIT, if possible. If not, patients received a short course of oral corticosteroids (n = 3 patients).⁹

Statistics

All data were analyzed by using statistical software (SPSS for Windows, version 11.0 [SPSS Inc, Chicago, Ill]). Medication score medians for groups were compared with Mann-Whitney *U* test and

TABLE I. Drug groups and generic names used in the birch pollen seasons (1999 and 2000), and the defined daily doses*

Drug group	Generic drug name	Concentration	Defined daily dose
Oral antihistamines			
	Acrivastine†	8 mg	1 capsule × 3
	Cetirizine‡	10 mg	1 tablet × 1
	Fexofenadine‡	120 mg	1 tablet × 1
	Astemizole	10 mg	1 tablet × 1
Nasal antihistamines			
	Levocabastine†	50 µg/dose	1 puff × 2
	Azelastine	1 mg/mL	1 puff × 2
Ocular antihistamines/ chromones			
	Levocabastine†	50 µg/dose	1 drop × 2
	Antazoline	5 mg/mL	1 drop × 2
	Emadastine	0.5 mg/mL	1 drop × 2
	Cromoglycate‡	20 mg/mL	1 drop × 4
Nasal corticosteroids			
	Beclometasone	50 µg/dose	1 puff × 2
	Fluticasone	50 µg/dose	1 puff × 2
	Triamcinolone	55 µg/dose	1 puff × 1
	Budesonide	64 µg/dose	1 puff × 2
Oral/intramuscular corticosteroids			
	Prednisolone†	5 mg/tablet	2.5 tablet × 1
	Methylprednisolone	40 mg/mL	2 mL §
Bronchial corticosteroids			
	Budesonide	200 µg/dose	1 inhalation × 2
Bronchial β ₂ -agonist			
	Salbutamol†	0.2 mg/dose	1 inhalation × 3
	Terbutaline‡	0.5 mg/dose	1 inhalation × 3

*Defined daily dose for optimal efficacy.¹²

†Season 2000, provided by the allergy clinic.

‡Season 2000, not provided by the allergy clinic.

§Once seasonally, intramuscular injection.

Wilcoxon signed-rank test. Intrarater (each patient) agreement was investigated by the Cohens weighted κ (κ_w).¹⁵ The κ equals 1.0 when agreement is perfect, and this is obtained along the diagonal of the matrix. The magnitude of disagreement increases with distance from the diagonal. It is generally accepted to quantify the strength of agreement as follows: $\kappa_w < 0$ (poor), 0 to 0.20 (slight), 0.21 to 0.40 (fair), 0.40 to 0.60 (moderate), 0.61 to 0.80 (substantial), and 0.81 to 1.00 (almost perfect).¹⁵ SE of κ_w could be calculated because $n \geq 2g^2$, where g equals the number of categories.¹⁵ The κ_w was tested against the null hypothesis, but κ_w differences between groups were not tested because the criterion of $n \geq 3g^2$ for comparison was not fulfilled.¹⁵

RESULTS

Patients and pollen counts

One female patient in the placebo group dropped out for unknown reasons, and 1 female patient in the SIT group was excluded because of noncompliance in diary completion. Missing data in the remaining diaries constituted less than 4%. The birch pollen counts in 1999 (duration of season, 19 days) and 2000 (season duration, 24 days) were representative for a low, respectively an average season.⁴ The birch symptom period lasted 29 days.

TABLE II. Agreement between in-seasonal reporting and out-seasonal recollection of drug groups used in-seasonally (n = 33 patients)

In-seasonal reporting	Out-seasonal recollection		κ_w^* (P value)
	Used	Not used	
Oral antihistamines (OAH)			
Used	28	2	.52
Not used	1	2	(<.005)
Nasal antihistamines (NAH)			
Used	21	3	.71
Not used	1	8	(<.00005)
Ocular antihistamines/ chromones (EAH)			
Used	26	2	.67
Not used	1	4	(<.0001)
Oral corticosteroids (OCS)			
Used	2	1	.78
Not used	0	30	(<.000005)
Inhaled β_2 -agonists (B β 2)			
Used	7	0	.77
Not used	3	23	(<.00001)
All drug groups (%)†			
Used	84 (50.9)	8 (4.9)	.83
Not used	6 (3.6)	67 (40.6)	(<.000001)

*Weighted κ , κ_w .†OAH + NAH + EAH + OCS + B β 2 (n = 5*33 pairs of agreement).

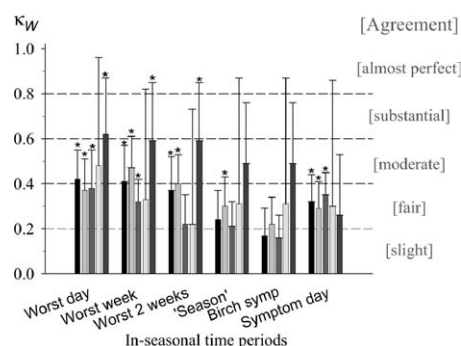
Data on symptom severity are reported elsewhere.⁹ Briefly, the SIT group reported significantly lower symptom severity in daily diaries,⁹ and only the SIT group had a significant reduction in recollected symptom severity.⁴

Agreement on drug groups used

Most patients chose to use the provided rescue medication (exceptions were cetirizine, n = 1; fexofenadine, n = 1; cromoglycate, n = 3; and terbutaline, n = 2), resulting in fewer drug types used in 2000 than in 1999 (Table I). Table II shows that the agreement between in-seasonal and out-seasonal reporting of drug group used was moderate to substantial (all P values < .05). Overall, the use of drug groups was almost perfect (Table II). There was no obvious difference between forgotten (n = 8) or erroneously recollected (n = 6) drug use, but no statistical method could be applied. Agreement on number of used drugs reported was substantial ($\kappa_w = 0.64$; $P < .0001$): the number of drugs was correctly recollected by 21, exaggerated by 5, and underestimated by 7 patients. In 1999, both groups recollected a median use of 3 (SIT, range 1-5; placebo, range 0-5) different drugs. In 2000, the SIT group used 2 (0-4) and the placebo group 3 (1-5) but without significant differences between or within groups.

Agreement on drug doses used

The best agreement on mean DD was observed for in-seasonal periods of 2 weeks (or shorter) with the highest drug consumption (Fig 1). For the season, all κ values except nasal antihistamine use were insignificantly

**FIG 1.** Agreement on mean daily drug doses: retrospective reporting compared with in-seasonally obtained daily mean for 6 periods. Columns from left to right: 1 (black) = oral antihistamine (AH); 2 (light grey) = nasal AH; 3 (intermediate grey) = conjunctival AH; 4 (lightest grey) = oral corticosteroid; 5 (darkest grey) = inhaled β -agonist. κ_w = Weighted κ . Bars = SEs. *Significantly different from agreement by hazard ($\kappa_w = 0$).

different from 0; thus, the null hypothesis could not be excluded. With increasing duration of the in-seasonal period, the out-seasonal mean DD significantly over-reported the use of oral and nasal antihistamines (Table III). We found no significant characteristics of subjects overestimating, underestimating, or correctly estimating their drug use.

Concerning gender, injection therapy, and the presence of grass pollinosis, agreement differed less than 1 SE (data not shown), but correct statistical testing of the difference between groups was not possible because of an insufficient number of patients.¹⁵

Ratings before and after immunotherapy

In Table IV, the median values of out-season reports of mean DD before (season 1999) and after (season 2000) SIT are presented. There were no significant differences at inclusion. At follow-up, the SIT group used significantly less oral antihistamines in 2000 than in 1999 and had a significantly lower total number of mean DDs than the placebo group.

DISCUSSION

A proper history on symptoms and medication in previous seasons is the basis when considering starting SIT.^{5,16} An objective registration of inhaled drug use is available,¹ contrary to registration of tablet use. Oral antihistamines are widely used for SAR, so we compared recollected drug use to self-reported drug use obtained prospectively in daily diaries—a validated method to document efficacy of intervention.⁵⁻⁸ We have previously published data on the useful recollection of symptom severity,⁴ which follows the same pattern as that for drug use recollection. First, we observed that recollection of kind of drugs used was almost perfect ($\kappa_w > 0.8$; Table II). We are not aware of any similar study. Second, we found that out-seasonal recollection agreed the best with the

TABLE III. In-seasonal period and out-seasonal overreporting/underreporting of in-seasonal drug doses used*

	Worst day	Worst week	Worst 2 weeks	Season	Birch period	P value†	Symptom day
Oral antihistamines	2/18	8/7	11/6	14/5	16/5	<.001	14/6
Nasal antihistamines	2/17	4/12	8/10	14/7	16/7	<.005	8/9
Ocular antihistamines/chromones	4/11	10/10	15/10	18/8	10/7	.11	11/9
Oral corticosteroids	0/2	1/2	1/2	1/2	1/2	.92	1/2
Inhaled β_2 -agonists	3/3	4/2	4/2	6/1	6/1	.57	6/2
P value‡	.1	.7	.8	.3	.2		.6

*Overreporting = out-seasonal drug use ratio > in-seasonal drug use ratio; underreporting = vice versa.

† χ^2 For trend (increasing number of days).

‡Mann-Whitney U test (difference between drug groups).

TABLE IV. Out-seasonal recollection of drugs and mean daily doses* taken during the season 1999 and 2000, median (range)

Drug group		1999	2000	P value‡
Oral antihistamines	SIT	0.58 (0.00-1.50)	0.31 (0.00-1.33)	.29
	Placebo	1.00 (0.00-2.00)	0.67 (0.04-1.00)	.32
	P value†	.44	.034	
Nasal antihistamines	SIT	0.00 (0.00-2.00)	0.02 (0.00-0.88)	.77
	Placebo	0.00 (0.00-1.50)	0.23 (0.00-1.00)	.12
	P value†	.96	.07	
Ocular antihistamines/chromones	SIT	1.00 (0.00-3.00)	0.21 (0.00-1.50)	.06
	Placebo	0.75 (0.00-1.50)	0.38 (0.00-1.50)	.35
	P value†	.79	.44	
Nasal corticosteroids	SIT	0.00 (0.00-2.00)	Drug group avoided in clinical study	—
	Placebo	0.00 (0.00-2.00)		
	P value†	.37		
Oral corticosteroids	SIT	0.00 (0.00-1.00)	0.00 (0.00-1.17)	.71
	Placebo	0.00 (0.00-1.00)	0.00 (0.00-0.29)	.66
	P value†	.53	.99	
Inhaled β_2 -agonists	SIT	0.00 (0.00-0.33)	0.00 (0.00-0.33)	.72
	Placebo	0.00 (0.00-0.33)	0.00 (0.00-1.00)	.48
	P value†	.71	.56	
Bronchial corticosteroids	SIT	0.00 (0.00-1.00)	Drug group avoided in clinical study	—
	Placebo	0.00 (0.00-1.00)		
	P value†	.40		
TOTAL	SIT	2.34 (0.16-5.33)	1.02 (0.00-4.25)	.007
	Placebo	2.25 (0.00-5.07)	1.42 (0.15-3.67)	.20
	P value†	.66	.14	

*Drug dose expressed relative to the defined daily dose (Table I). SIT group, n = 16; placebo group, n = 16.

†Mann-Whitney U test.

‡Wilcoxon signed-rank test.

mean DD during the day, the week, or 2 weeks with the largest drug consumption (Fig 1). However, the number of cases was too low to allow statistical testing of differences between the in-seasonal periods.¹⁵ Interestingly, we found almost no agreement ($\kappa_w = 0$) with the mean DD used in the season. Instead, we found a tendency of out-seasonal overreporting. In studies on antiviral therapy for AIDS, the agreement was lower ($\kappa_w = 0.3$ -0.5) but also highest for periods <14 days in duration.^{2,3} Similarly, Bender et al¹ found that during a 6-month period, the recollected inhaled steroid use was 60% greater than that measured electronically on inhaler devices. This overreporting

probably reflects that irrespective of seasonal or chronic nature, patients remember symptom severity and actions taken when disease interferes the most with normal daily life.^{4,17-19} Third, we observed that out-seasonal recollection of mean DD was sufficiently sensitive to detect the effect of intervention, but only on oral antihistamine and total drug doses used (Table IV). We have previously published that the SIT group used significantly less of exactly these 2 drugs on the basis of intergroup comparison of the diaries.⁹ Changing the patients' habitual drugs to the study rescue medication (Table I) might theoretically have lowered the recollection of drug family and/or

doses. In Denmark, pharmacies are ordered to dispense the cheapest alternative of pharmacologically identical products; thus, patients rarely receive the same drug brand for several years. Furthermore, we provided the patients with repeated instructions in the rational use of each drug to increase self-management. This is probably reflected in the data in Table IV, where the placebo group had a decrease, although insignificant, in drug consumption despite a higher pollen load.

Subjects allergic to grass pollen who had interposed allergic symptoms between birch season and recollection of drug use had κ values within the SE of the patients allergic to birch pollen exclusively. Again, the number of cases was too low to allow statistical testing of differences between groups.¹⁵

The transformation of discrete data into categories, the grouping of drugs into families, and the fusion of conjunctival antihistamines and chromones naturally imply some loss of information.²⁰ However, we chose a pragmatic view: do patients recollect whether they used no, little, intermediate, or maximal dose of a drug with a certain pharmacological action relevant in SAR treatment (drug groups listed in Table I)?^{13,14} In any case, the agreement should increase rather than fall, because the fewer categories, the higher the agreement.¹⁵ The use of a ratio between mean DD and daily defined use is questionable but allowed the addition into a total number of defined daily doses taken (Table IV). We hope that our study may inspire future studies in the issue.

In conclusion, retrospective recollection of drug group used was almost perfect. Out-seasonal reporting of the daily drug dose describes a shorter period than the pollen season. In an intervention study, out-seasonal ratings were sufficiently sensitive to detect the effect of SIT, but only on decreased oral antihistamine use and total drug use.

We thank all patients for their exquisite patience, and the study nurse, Anne-Sofie Lassen, for practical assistance.

REFERENCES

- Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefer S, Milgrom H, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Ann Allergy Asthma Immunol* 2000;85:416-21.
- Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* 2002;16:269-77.
- Gao X, Nau DP. Congruence of three self-report measures of medication adherence among HIV patients. *Ann Pharmacother* 2000;34:1117-22.
- Bodtger U, Poulsen LK, Mallng HJ. Retrospective assessment of seasonal allergic symptoms: over-rating but useful. *Clin Exp Allergy* 2003;33:496-500.
- Bousquet J, Lockey R, Mallng HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases: a WHO position paper. *Allergy* 1998;53(suppl 44):1-42.
- Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302:265-9.
- Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszc M, Blaser K, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003;33:1205-14.
- Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of allergic rhinitis symptoms in an adult Danish population. *Allergy* 1999;54:1194-8.
- Bodtger U, Poulsen LK, Jacobi HH, Mallng HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy: a one-year, randomised, double-blind, placebo-controlled study. *Allergy* 2002;57:297-305.
- Hodal L, Rasmussen A. [Measurements of pollen and spores in Denmark: season 1999]. Report number 00-12. Copenhagen, Denmark: AAF and DMI; 2000.
- Winther L, Mallng HJ, Moseholm L, Mosbech H. Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis, I: efficacy estimated by a model reducing the bias of annual differences in pollen counts. *Allergy* 2000;55:818-26.
- Pedersen C, Bjerrum L, Friis H, Hendel J, editors. *Lægemiddelkataloget [Danish Index of Pharmaceutical Drugs, 2004]*. 29th ed. Copenhagen, Denmark: Dansk Lægemiddel Information A7S; 2004 (based on the ATC Index with DDDs 2004. WHO Collaboration Centre for Drug Statistics and Methodology, Oslo).
- Bousquet J. Global initiative for asthma (GINA) and its objectives. *Clin Exp Allergy* 2000;30(suppl 1):2-5.
- Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(suppl 5):S147-334.
- Kramer MS, Feinstein AR. Clinical biostatistics, LIV: the biostatistics of concordance. *Clin Pharmacol Ther* 1981;29:111-23.
- Druce HM. Allergic and non-allergic rhinitis. In: Middleton EJR, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. *Allergy: principles & practice*. St Louis: Mosby-Year Book, Inc; 1998. p. 1005-16.
- Sawyer SM, Aroni RA. Sticky issue of adherence. *J Paediatr Child Health* 2003;39:2-5.
- Feine JS, Lavigne GJ, Dao TT, Morin C, Lund JP. Memories of chronic pain and perceptions of relief. *Pain* 1998;77:137-41.
- Porzelius J. Memory for pain after nerve-block injections. *Clin J Pain* 1995;11:112-20.
- Svensson E. Concordance between ratings using different scales for the same variable. *Stat Med* 2000;19:3483-96.