2002-210-1

Patient Compliance in Rheumatoid Arthritis, Polymyalgia Rheumatica, and Gout

ERIK de KLERK, DÉSIRÉE van der HEIJDE, ROBERT LANDEWÉ, HILLE van der TEMPEL, JOHN URQUHART, and SJEF van der LINDEN

ABSTRACT. ***Objective.*** (1) To explore patient compliance with prescribed drug regimens in the setting of usual care for outpatients with rheumatoid arthritis (RA), gout, and polymyalgia rheumatica (PMR) by utilizing electronic medication event monitors (MEMS®) to register openings of the medication package. (2) To examine the influence of disease, frequency of intake of the drug, and class of drug on compliance. (3) To explore the influence of demographic factors, quality of life measures, coping, health status, and functional ability as potential predictors of patient compliance.

Methods. A total of 127 consenting consecutive patients were enrolled: 81 patients with RA, 33 taking nonsteroidal antiiflammatory drugs (13 diclofenac TID and 20 naproxen BID) and 48 taking disease modifying antirheumatic drugs [25 sulfasalazine (SSZ) BID and 23 methotrexate (MTX) once weekly]; 17 patients with PMR starting with prednisolone QD; and 29 patients with gout starting with colchicine (12, QD) or starting with uric acid lowering agents (17, QD). All patients received first prescriptions and were instructed to take the medication as prescribed. Followup was 6 months (gout 12 mo). All patients were aware of the monitoring capability of the package. At baseline a series of questionnaires was completed. We summarized the dosing histories as "taking compliance" (percentage of total prescribed doses taken), "correct dosing" (percentage of doses taken as prescribed), and "timing compliance" (percentage of doses taken within +/– 25% of prescribed interdose intervals).

Results. A total of 26,685 days (> 73 patient-years) were monitored. Compliance expressed as "taking compliance," mean (95% CI), "correct dosing," mean (95% CI), and "timing compliance," mean (95% CI) are: naproxen: 82% (75–90), 68% (57–80), 48% (34–61); diclofenac: 77% (61–93), 67% (47–87), 39% (21–57); MTX: 107% (98–117), 81% (75–87), 83% (76–90); SSZ: 72% (60–84), 55% (44–67), 25% (18–33); prednisolone: 96% (89–102), 88% (83–92), 82% (74–89); colchicine: 65% (48–81), 44% (26–62), 32% (18–46); and uric acid lowering agents: 84% (76–92), 74% (63–85), 65% (52–79). Missed doses occurred more frequently than taking of extra doses: in RA, on 10% of all monitored days there was no evidence of dosing, while on 3% of all monitored days extra doses were taken. In PMR and gout these data are 10% and 4%, and 15% and 7%, respectively. We observed a decline of compliance over time in all study medication groups. Multiple regression analyses showed that the class of medication (symptom modifying or disease controlling), the dosing frequency, the patient's sex, coping pattern (avoidance, passive reaction pattern, and expression of emotions), and the overall health (total Nottingham Health Profile score) together explained 67% of the variance in taking compliance (adjusted R^2) ($p = 0.002$).

Conclusion. Studying patient compliance with prescribed drug regimens utilizing electronic medication event monitors in RA, gout, and PMR showed that large differences exist in compliance between the various medication groups. Compliance declines over time. A regression model shows that it is possible to relate differences in patient compliance to a number of medication and patient related factors. (J Rheumatol 2003;30:44–54)

Key Indexing Terms:
PATIENT COMPLIANCE | RHEUMATOID ARTHRITIS | GOUT
POLYMYALGIA RHEUMATICA | DRUG THERAPY

From the Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, Maastricht, The Netherlands; Limburg University Center, Diepenbeek, Belgium; Department of Rheumatology, Maasland Hospital Sittard, Sittard; and Department of Epidemiology, Maastricht University, Maastricht, The Netherlands.

Supported by grant NR 831 from the Dutch Arthritis Association (Nederlands Reumafonds).

E. de Klerk, MD, MSc, Scientific Researcher; R. Landewé, MD, PhD, Rheumatologist; S. van der Linden, MD, PhD, Professor of Rheumatology, Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht; D. van der Heijde, MD, PhD, Professor of Rheumatology, Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, and Limburg University Center; H. van der Tempel, MD, Rheumatologist, Department of Rheumatology, Maasland Hospital Sittard; J. Urquhart, MD, FRCP (Edin), Professor of Pharmaco-Epidemiology, Department of Epidemiology, Maastricht University.

Address reprint requests to Dr. D. van der Heijde, Division of Rheumatology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: dhe@sint.azm.nl

Submitted March 6, 2002; revision accepted June 12, 2002.

Compliance with treatment guidelines or standards by health professionals and compliance with prescribed drug regimens by patients are major determinants of outcome[1,2]. In daily practice reduced compliance is a well known but poorly understood phenomenon. Data on drug regimen compliance by patients in rheumatology are scarce. A study among patients with ankylosing spondylitis revealed that deviations from the prescribed once-daily regimen of a nonsteroidal anti-inflammatory drug (NSAID) occurred frequently, even in the setting of a randomized clinical trial[3].

We investigated patient compliance with prescribed drug regimens in the setting of usual care for outpatients with one of 3 rheumatological diseases: rheumatoid arthritis (RA), gout, or polymyalgia rheumatica (PMR). The dosing frequency called for by the drug regimens varied between "3 times daily" and "once weekly." The drugs prescribed differ in their actions. Some have "direct symptom-modifying effects," others are intended for use as "late onset disease-controlling therapy" or "preventive therapy." Prednisolone was used as a drug that has both symptom-modifying and disease-controlling effects.

We used electronic medication event monitoring devices to document patient compliance with drug therapy, because this method addresses several aspects of patient compliance[4,5]. This method is widely considered the standard for compiling drug dosing histories of ambulatory patients[6-8].

We describe compliance with naproxen, diclofenac, sulfasalazine (SSZ), and methotrexate (MTX) in RA, prednisone in PMR, and colchicine, allopurinol and uricosurica in gout. We examine the influence of disease, frequency of intake of the drug, and indication (direct effects versus late onset of effectiveness) on patient compliance. In addition we explore the influence of a number of demographic factors, quality of life measures, coping, health status, and functional ability as potential predictors of patient compliance.

MATERIALS AND METHODS

The study was conducted as a series of cohort studies. We included all consecutive consenting outpatients with a diagnosis by a rheumatologist of RA, PMR, or gout at the outpatient rheumatology clinics of University Hospital Maastricht, Atrium Hospital Heerlen, and Maasland Hospital Sittard, respectively, a secondary/tertiary and 2 secondary referral centers for rheumatology. For all studies, approval was obtained from the Medical Ethical Committee of all 3 hospitals.

Patients with RA were to be included when the rheumatologist prescribed SSZ (BID, after up-titration) or oral MTX (once weekly), or if the rheumatologist prescribed either diclofenac (TID or combined with misoprostol BID) or naproxen (BID). Patients with a diagnosis of PMR were included if they received prednisone or prednisolone QD. In the analyses, patients taking prednisone and prednisolone were combined and we will continue to use the term prednisolone for this group. Patients with a diagnosis of gout were included if the rheumatologist prescribed longterm prophylactic maintenance therapy with colchicines (QD) or uric acid lowering agents such as allopurinol or benzbromaron (QD). In the analyses, patients taking allopurinol or benzbromaron were combined in a single group, called uric acid lowering agents.

All prescriptions in all diagnoses had to be first prescriptions (which did not necessarily mean a newly determined diagnosis) and had to be written "to be taken as directed" (not "on demand"). We further required that the treating rheumatologist expected that drug treatment would continue for at least 6 months.

To measure patient compliance we used the Medication Event Monitoring System (MEMS®, Aardex, Zug, Switzerland). It consists of a cup-type medication container with a threaded, screw-cap closure. Within the closure is microelectronic circuitry to record time and date of each opening and closing of the medication package. The method, with its advantages and disadvantages, has been discussed in detail[6-12].

The rheumatologist informed eligible patients about the purpose of the project and the operation of the MEMS. A demonstration was given of how the system worked. Patients were then asked to sign the informed consent document. Each patient then received a MEMS, and the patient's pharmacist was notified by fax that the patient was entered in a research project and asked to transfer the prescribed medication to the MEMS container. Patients also received a set of questionnaires (see below), which they were asked to complete in the first week after start of the medication. All patients received a followup phone call by the investigator (EdK) about 3 days after the visit to the rheumatologist to answer questions, and to ensure that the medication was indeed transferred to the MEMS container.

Six months after start of drug therapy (12 months in the patients with gout) or sooner if patient or rheumatologist stopped medication, patients were asked to complete a second set of questionnaires, identical to the first set, and to return the MEMS container to the rheumatologist or investigator. In addition, patients were asked to provide a prescription drug history, which they obtained from their pharmacy. This is a computerized list containing all dates and drugs dispensed at the patient's pharmacy. In The Netherlands the majority of patients are required to subscribe to one pharmacy, ensuring that most if not all dates of medication dispensing (and therefore extra openings) were recorded[13]. The data of the MEMS were downloaded via a MEMS-communicator to a Windows® based personal computer, and analyzed by software designed to analyze dosing histories (CSS version 2.1, Aardex, Zug, Switzerland).

Each patient's data were compared with the prescription drug history and, if available, remarks of the patient and, if necessary, days of special openings (such as pharmacy visits or if the patient had recorded openings unrelated to treatment). These extra openings were marked as a non-monitored period. This procedure ensures that the calculation of the compliance summary variables (see below) is as free as possible of artifacts unrelated to actual medication taking.

The dosing histories were transformed to the following categories.

(1) Taking compliance: The percentage of prescribed doses taken, calculated as:

(total number of recorded medication events / total number of prescribed doses) × 100%

Example: a patient opened and closed the MEMS container 170 times while prescribed SSZ BID for a monitored period of 100 days, so taking compliance = (170 / 200) × 100% = 85%.

Taking compliance is useful as an overall compliance variable. However, it is rather crude, as no information on the timing of doses is incorporated, and omitted doses occurring at one time can be obscured by extra doses taken at another time.

(2) Correct dosing: The percentage of days within which the correct number of doses were taken, calculated as:

(total number of days with recorded medication events as prescribed / total number of monitored days) × 100%

Example: a patient who had been prescribed SSZ BID has a dosing history, compiled by the MEMS, that showed 170 medication events during a monitored period of 100 days, but only 58 of the monitored days showed 2 medication events. Thus, correct dosing = (58 / 100) × 100% = 58%.

Correct dosing is a useful variable to determine actual day-by-day drug use. It incorporates day-by-day variability in dosing, and is not influenced by "catch-up" dosing. It is stricter than taking compliance.

(3) Timing compliance: We allowed the patients to vary the interdose-inter-

vals within an arbitrarily chosen plus or minus 25%. Thus, for a QD regimen, the prescribed interval is 24 hours, but we allowed intervals of 18–30 hours. Similarly, for a BID regimen we allowed intervals of 9–15 hours, for a TID regimen we allowed intervals of 6–10 hours, and for a once-weekly regimen we allowed intervals of 126–210 hours. Timing compliance was then calculated as:

(the number of interdose-intervals of allowed duration / number of prescribed interdose-intervals) × 100%

Note that if there are missed doses, the number of interdose-intervals is by definition lower than the number of prescribed interdose-intervals, so timing compliance does not necessarily add up to 100%.

Example: a patient who had been prescribed SSZ BID has a dosing history, compiled by the MEMS, of 170 medication events during a monitored period of 100 days, but only 45 of all interdose-intervals were between 18 and 30 hours' duration. Timing compliance is: (45 / 199) × 100% = 22.6%.

Timing compliance determines interdose-intervals, which, when excessively long, may indicate periods of time when drug action was subtherapeutic or absent. It is a stricter measure of compliance with the prescribed drug regimen than correct dosing.

Questionnaires. The questionnaires consisted of some demographic questions: age, sex, education (low = primary school, intermediate = secondary school, high = further education), profession (employed or not), and social support (living alone, with partner, with partner and children). We also asked patients to complete the Health Assessment Questionnaire (HAQ)[14], Nottingham Health Profile (NHP)[15], Utrecht Coping List (UCL)[16], European Quality of Life measure (EuroQol)[17], Long Term Medication Behavior Self-Efficacy Scale (LTMBS)[18], a self-composed list of 40 frequent side effects, and for RA patients only, the Rheumatoid Arthritis Quality of Life measure (RAQol)[19-21].

HAQ scores range from 0 (minimum) to 3 (maximum)[14]. The NHP scores were summed and computed into 6 subscales: energy, pain, emotional reactions, sleep, social isolation, and physical mobility[15]. For the UCL, 7 subscales were computed: active attitude, palliative reaction, avoidance, seeking social support, passive reaction pattern, expression of emotions, and comforting thoughts[16]. The EuroQol describes health status in 3 levels: 1 = no problem, 2 = some problems, 3 = extreme problems. It also includes a self-rated thermometer indicating the patient's own assessment of their health state[17]. The LTMBS is a 26 item questionnaire designed to measure self-efficacy for patients undergoing chronic drug therapy. The results were summed and calculated to a scale ranging from 0 (lowest possible self-efficacy) to 100 (highest possible self-efficacy)[18,22]. The RAQol ranges from 0 (worst possible quality of life) to 30 (perfect quality of life)[19-21].

As no standard instrument was available at the time of the start of the study to document side effects of drug treatment in rheumatology, we devised a measure with 40 questions for the most common side effects associated with naproxen, diclofenac, SSZ, MTX, prednisone, colchicine, allopurinol, and benzbromaron. The frequencies of side effects were based on US FDA approved labeling for each of these products, as compiled in the *Physicians Desk Reference*[23]. Each question consisted of 2 parts: occurrence (never = 0, sometimes = 1, frequently = 2, often = 3, always = 4) and, if the answer was anything other than "never," patients were asked to rate the severity on a range from 1 (not disturbing at all) to 5 (very disturbing). A frequency of side effects score was computed by summing the 40 items of occurrence into one variable (range 0 = no side effects at all, 160 = maximum frequency of side effects score). In addition, a total side effects score was calculated as (occurrence × frequency), ranging from 0 (no side effects at all) to a maximum of 800 (maximum occurrence and severity of side effects).

Statistics. Analyses consisted of descriptive statistics (means, standard deviations, 95% confidence intervals), Pearson's correlation coefficients, (stepwise) multiple regression analyses with adjustment for multiple variable testing, one-way analysis of variance with the Scheffé multiple comparison test for post-hoc analysis, and, where appropriate, nonparametric alternatives. All analyses were performed using SPSS version 10.0.7 for Windows.

RESULTS

Compliance on the individual level

It is often useful to convert the dosing histories from the electronic monitors to calendar and chronology plots for a quick overview of the patient's dosing history. The calendar plot (an example is shown in Figure 1) shows the number of recorded doses on each day of the study period. It is helpful to identify periods in which dosing was not optimal, and to correlate clinical events (such as the occurrence of flares, gout attacks, or specific adverse drug reactions) to specific dates. However, the calendar plot does not give details on within-day timing of drug intake, and only roughly shows changes in the patient's dosing pattern over time. Such information is shown by the chronology plot (4 examples are shown in Figure 2). From these plots it becomes apparent that patient compliance on drug therapy is a day-by-day phenomenon, which in some instances is difficult to grasp in a single summary variable.

Overall compliance results

We studied 127 consenting consecutive patients of the outpatient clinic. They consisted of 81 patients with RA using NSAID (13 diclofenac and 20 naproxen) or DMARD (25 SSZ and 23 MTX), 17 patients with PMR taking prednisone, and 29 patients with gout taking colchicine (12) or allopurinol (10) or benzbromaron (7). A total number of 26,685 days were monitored (> 73 patient-years). The mean followup was 210 days. Table 1 summarizes the demographic data.

RA — NSAID. Figure 3 depicts the taking compliance, correct dosing, and timing compliance of the various drugs between the 3 diagnoses, along with the corresponding 95% confidence intervals. There are clear and statistically significant differences between the drugs (Table 2). Compliance reports with naproxen and diclofenac were comparable, with a taking compliance of 82% and 76%, correct dosing of 68% and 67%, and timing compliance of 48% and 39%, respectively.

RA — DMARD. There were large differences between the DMARD, however. Taking compliance for SSZ was 72%, for MTX 107%. This difference was statistically significant ($p <$

August 1998

	Mon	Tue	Wed	Thr	Fri	Sat	Sun
						0	1
3	1	1	1	1	0	0	1
10	1	1	1	1	1	1	1
17	1	1	1	1	1	1	1
24	1	0	1	1	1	0	1
31	1						

Figure 1. Example of a calendar plot. This gout patient, prescribed allopurinol QD, told us that he likes to go out on the weekends and thought that allopurinol and alcohol did not go together well. Hence he would not take it on most Saturdays. See Figure 2 for the chronology plot (Patient 2046).

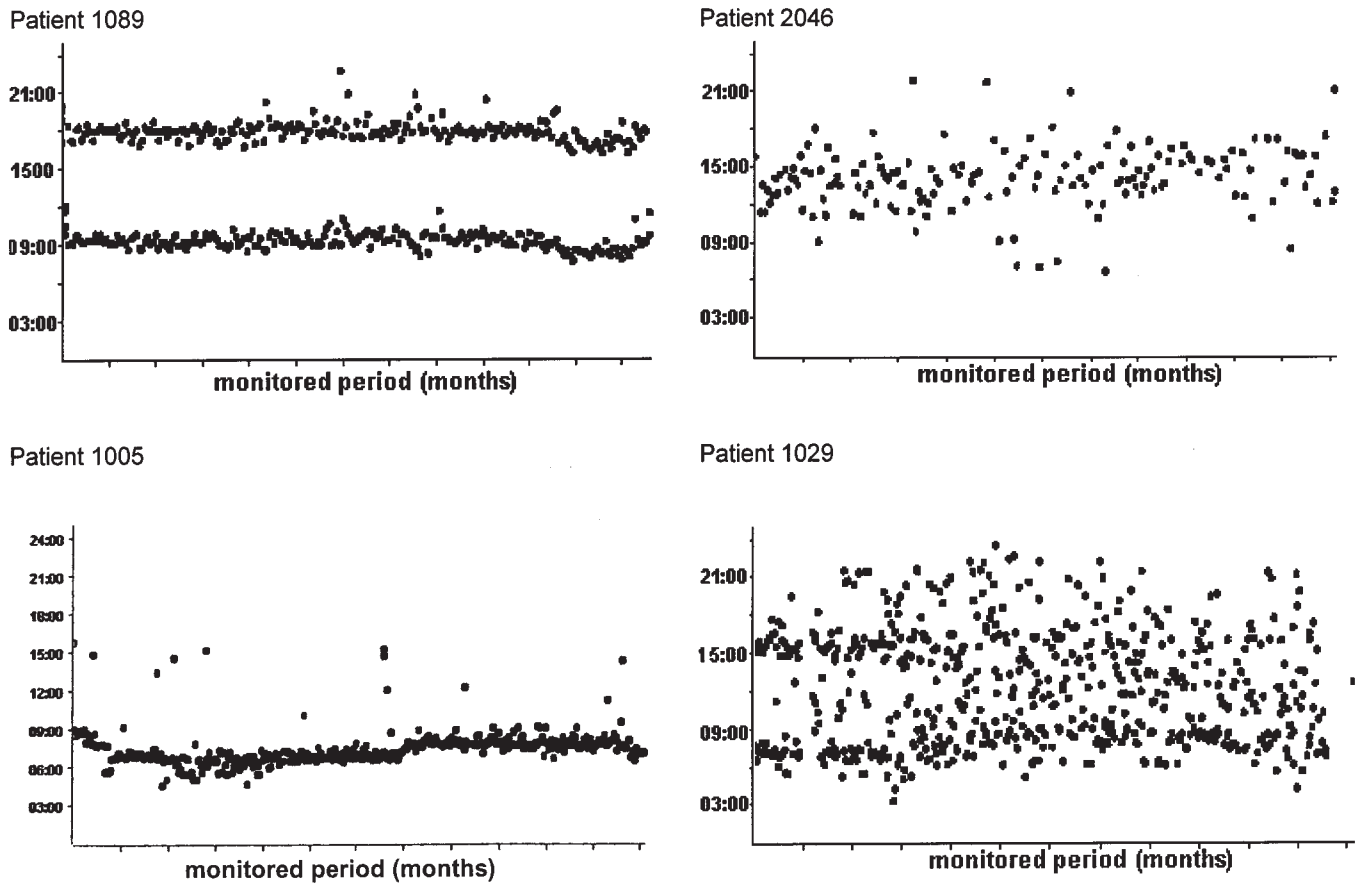

Figure 2. Example of 4 chronology plots. Patient 1089 is a patient with RA taking BID SSZ. She is taking almost 100% of the drugs, but is taking the doses in relatively short intervals, resulting in a lower timing compliance (25%). Patient 2046 is a gout patient taking QD allopurinol (see Figure 1), frequently missing doses on weekends. Patient 1005 is a patient with PMR prescribed QD prednisone. She frequently takes extra doses, but hardly ever misses a dose. Patient 1029 is a gout patient taking BID maintenance therapy with colchicine. Even though taking compliance is good at 84%, he is taking the correct number of doses on 60% of the days, and only 20% of all doses are within the prescribed interdose-interval.

Table 1. Demographic data.

	RA, n = 81	PMR, n = 17	Gout, n = 29
Age, yrs, mean (SD)	60 (14)	72 (7)	58 (12)
Sex, % female	66	76	20
Social support, %			
Single	29	24	17
Married/living together without children	64	70	80
Married/living together with children	7	6	3
Education, %			
Low	28	24	17
Intermediate	64	71	80
High	7	6	3
Work, % working	26	12	54

0.001). A comparable picture emerges from the comparison of correct dosing and timing compliance between the DMARD — correct dosing: SSZ 55%, MTX 81% ($p < 0.001$); and timing compliance: SSZ 25%, MTX 83% ($p < 0.001$).

PMR. Compliance with prednisolone among PMR patients was high: taking compliance 96%, correct dosing 88%, and timing compliance 82%. Confidence intervals around the mean were relatively small compared to other drugs, indicating little interpatient variability.

Gout. The compliance of PMR patients prescribed systemic steroids contrasted quite sharply with the compliance of the gout patients. In particular, compliance for maintenance colchicine therapy was strikingly low: taking compliance 65%, correct dosing 44%, and timing compliance 32%. Compliance with the combined uric acid lowering agents was better: taking compliance 84%, correct dosing 74%, and timing compliance 54%.

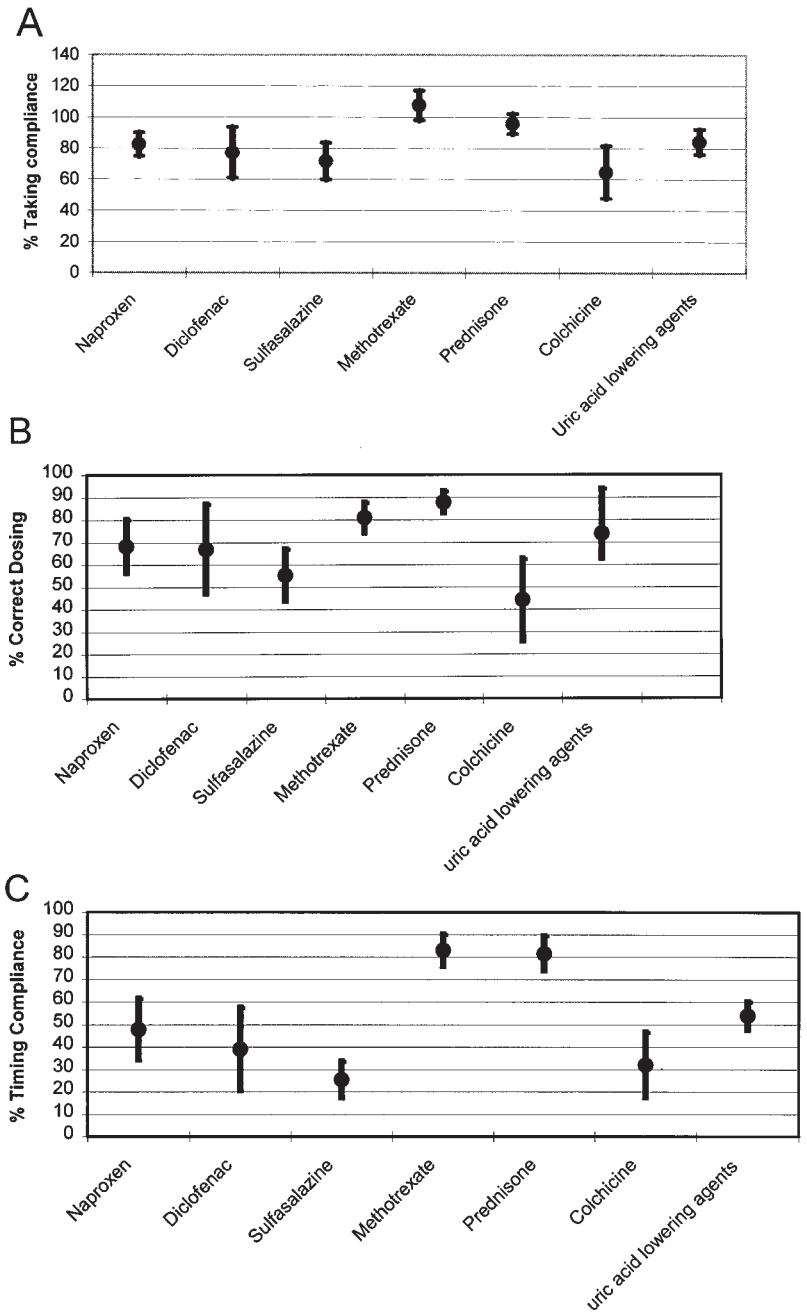

Figure 3. A. Taking compliance. B. Correct dosing. C. Timing compliance.

Figure 4 shows the distribution of taking compliance, correct dosing, and timing compliance when the proportion of patients is plotted against compliance organized in categories of 10% each. The distribution follows the previously described "typical J-shaped compliance distribution"[4,24]. It is clear, however, that for correct dosing and timing compliance, the peak of the J-shaped distribution is further skewed to the left, indicating a larger number of patients whose compliance is suboptimal. We also rank-ordered individual patients according to taking compliance, correct dosing, and timing compliance (Figure 5). As expected, in general, timing compliance is worse than correct dosing, which in turn is worse than taking compliance.

Missed doses occurred more frequently than taking of extra doses: in RA, on 10% of all monitored days there was no evidence of dosing, while on 3% of all monitored days extra doses were taken. In PMR, missed and extra doses were 10% and 4% of all monitored days, and in gout they were 15% and 7%, respectively. We further divided missed doses into "occasionally missed" (periods of 1 or at most 2 consecutive days

Table 2. Diagnosis, patient commpliance, and drug regimen.

Diagnosis	Drug	Dosing Frequency	Indication	Symptom Modifying/ Disease Controlling Drug	Taking Compliance, %	Correct Dosing, %	Timing Compliance, %
RA	Naproxen (n = 20)	BID	Pain	SM	82	68	48
	Diclofenac (n = 13)	TID	Pain	SM	76	67	39
	Sulfasalazine (n = 25)	BID	Inflammation	DC	72	55	25
	Methotrexate (n = 23)	Once weekly	Inflammation	DC	107	81	83
PMR	Prednisolone (n = 17)	QD	Inflammation	SM + DC	96	88	82
Gout	Colchicine (n = 12)	QD	Preventive	DC	65	44	32
	Allopurinol/ benzbromaron (n = 17)	QD	Lower urate	DC	84	74	62
					F = 7.13, p < 0.001*	F = 5.98 p < 0.001*	F = 19.1, p < 0.001*

* One-way ANOVA.

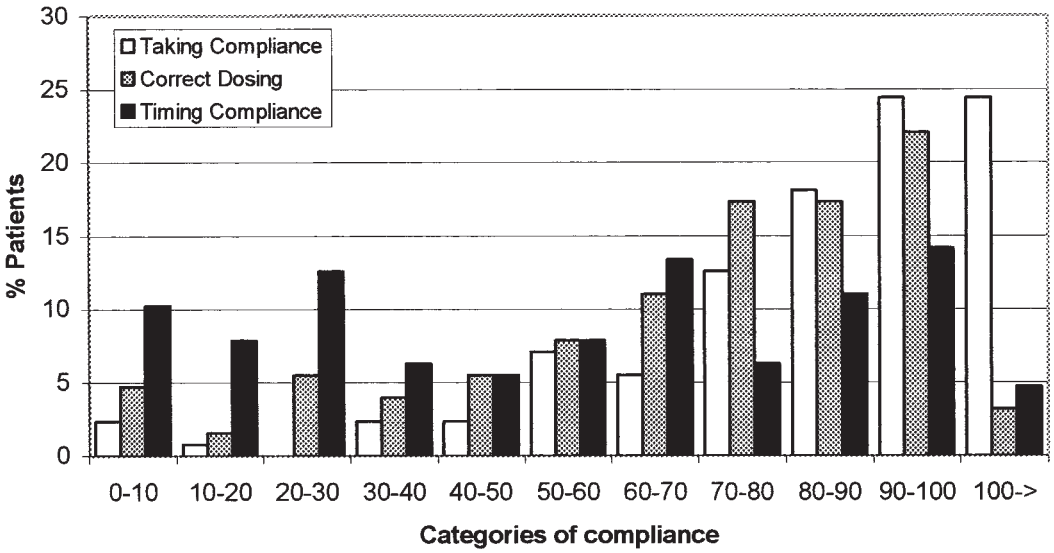

Figure 4. Distribution of taking compliance, correct dosing, and timing compliance.

without dosing) and "drug holidays" (periods of 3 or more consecutive days without dosing)[25,26]. Drug holidays were not computed for the patients taking MTX because of the weekly dosing regimen. There were a total of 192 drug holidays. Patients taking SSZ, colchicine, and uric acid lowering agents had the highest frequency of drug holidays (2.4–2.5 per patient), while all other groups had roughly 1–1.2 drug holidays per patient.

There were clear and statistically significant differences in compliance between the 4 dosing regimens (Figure 6). Compliance with once-weekly (all RA patients taking MTX) was the best, followed by QD, then BID and TID, for taking compliance, correct dosing, and timing compliance. Three separate ANOVA showed that these differences were statistically significant (all $p < 0.001$).

All groups showed a gradual and large decline of compliance over time. Comparison of compliance in the first month versus compliance in the 6th month showed an overall decline

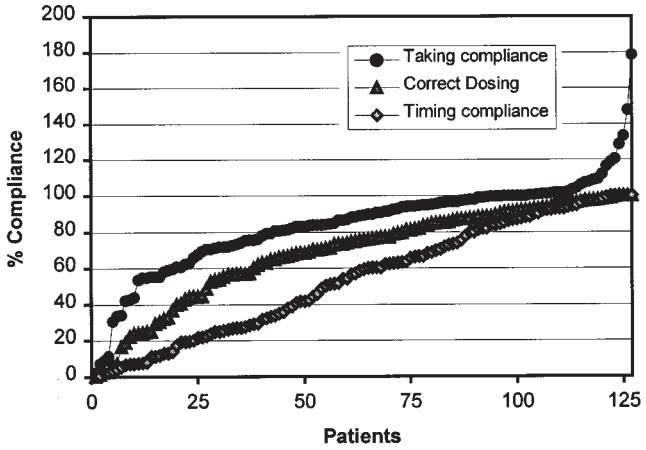

Figure 5. Patients rank-ordered by taking compliance, correct dosing, and timing compliance.

of 22% (Figure 7). Although the between-drug differences were large, none reached statistical significance.

Determinants of compliance

Functional capacity. HAQ total score was 0.75 ± 0.68. There were statistically significant differences in HAQ scores between the 3 diseases: RA patients had the highest scores (0.87 ± 0.72), then PMR patients (0.68 ± 0.67), and gout patients showed the lowest scores (0.44 ± 0.44). These differences were statistically significant (chi-square 8.24, p = 0.02). There was no correlation of HAQ scores or of HAQ category scores (data not shown) with taking compliance, correct dosing, or timing compliance. This was also true within each of the 3 diseases. In addition, a one-way ANOVA of the HAQ total score, with taking compliance, correct dosing, and timing compliance as separate independent variables, did not show any statistically significant differences. These results indicate that functional capacity, as measured by HAQ total score, seem not to be associated with patient compliance.

Overall health profile. The NHP total score at baseline was 11.6 ± 7.8. There were no differences between the drugs or the diseases. The NHP baseline subscores were as follows: energy 0.03 ± 0.03; pain 0.30 ± 0.20; emotional reactions 0.16 ± 0.21; social isolation 0.02 ± 0.04; sleep 0.09 ± 0.08; and physical mobility 0.23 ± 0.18. Neither taking compliance, correct dosing, nor timing compliance were associated with the total score, although the subcategories were statistically significantly associated with taking compliance (F = 2.50, p = 0.03), correct dosing (F = 2.30, p = 0.04), and timing compliance (F = 2.08, p = 0.06). These findings suggest that some NHP baseline subscores are predictive of compliance during the study period.

Coping. The UCL subscores were (mean ± SD): active attitude 17.5 ± 5.6; palliative reaction 18.5 ± 5.4; avoidance 17.1 ± 5.4; seeking social support 12.7 ± 4.4; passive reaction pattern 11.3 ± 3.9; expression of emotions 5.5 ± 2.3; and comforting thoughts 13.1 ± 3.2. There were no differences between UCL subscores within the drugs, diseases studied, or categories of compliance.

Perceived health status. There were no between-disease differences in baseline overall health status as measured by the EuroQol visual analog scale (VAS). Compliance scores between patients who rated their health status as worse during the prestudy period were statistically significantly higher compared with those of patients who rated their health status as the same or better during the prestudy period (Table 3). In addition, the VAS that is part of the EuroQol showed a statistically significant association with taking compliance (F = 4.32, p = 0.04). The association was negative, meaning that the better the perceived health state at the beginning of the study, the lower the compliance during the study. The strength of the association (R^2 = 0.04) was negligible, however.

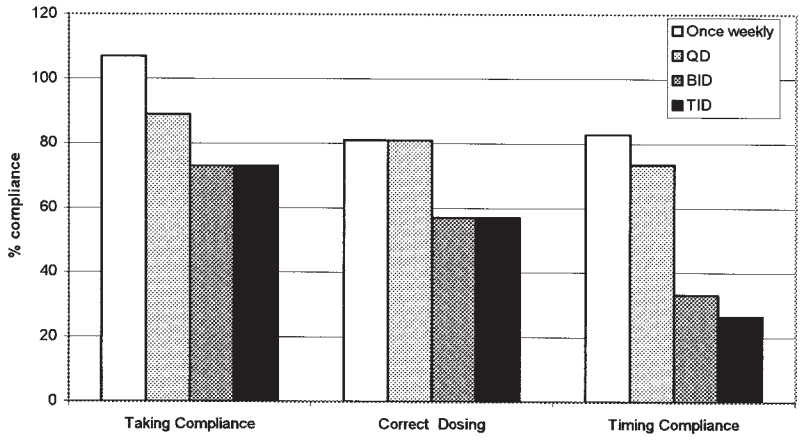

Figure 6. Influence of dosing regimen on compliance. QD: once daily, BID: twice daily, TID: 3 times daily.

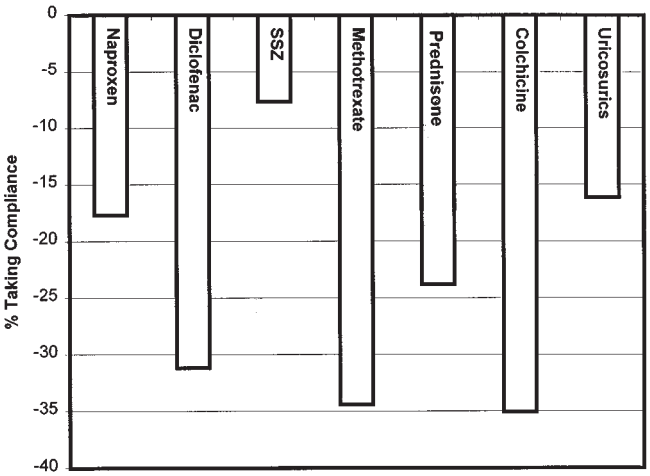

Figure 7. Decline of compliance over time.

Table 3. EuroQol health status at baseline.

	Better, n = 20	Same, n = 62	Worse, n = 61
Taking compliance, %	81	78	95*
Correct dosing, %	69	61	79**
Timing compliance, %	43	46	66†

* Statistically significant: F = 5.42, p < 0.01. ** Statistically significant: F = 6.00, p < 0.01. † Statistically significant: F = 5.25, p < 0.01.

Self-efficacy. The average LTMBS total score was 89.5 (SD 9.13), indicating high levels of self-efficacy. There were statistically significant between-disease differences in self-efficacy (chi-square 7.96, p = 0.02): patients with PMR had higher levels of self-efficacy (mean 96 ± 5), whereas patients with gout had lower levels (86 ± 11). Total self-efficacy was statistically significantly associated with taking compliance (F = 5.9, p = 0.02), but not with correct dosing or timing compliance. In addition, the explained variance of total self-efficacy score on taking compliance was low (R^2 = 0.07). Further, the associations of individual LTMBS items with taking compliance, correct dosing, and timing compliance were not statistically significant.

Drug related side effects. From the self-devised questionnaire for side effects, we noted 107 patients (84%) reporting at least one side effect. The average was 3.3 side effects (SD 5.0), with a minimum of 0 and a maximum of one patient who reported 25 side effects. The severity was 16.5 (SD 20.7), while the frequency × severity of side effects was 6.4 (SD 11.0). There was no association between frequency or severity or the combination of both with taking compliance, correct dosing, or timing compliance. In addition, no individual items on the side effects measure were associated with any compliance summary variable.

RA quality of life. Within patients with RA, there were no differences in RAQol total score between the 4 drugs or between the 2 drug groups (symptom modifying and disease controlling). The RAQol total score and its individual items did not show any association with taking compliance (F = 0.21, p = 0.65 and F = 1.0, p = 0.50, respectively), correct dosing (F = 0.34 with p = 0.56 and F = 0.86 with p = 0.66), or timing compliance (F = 0.05 with p = 0.94 and F = 0.86 with p = 0.66). We therefore conclude that RAQol total score is not associated with compliance.

A multiple regression model with taking compliance as dependent variable and backward elimination of the demographic and questionnaire variables showed that the class of medication (symptom modifying or disease controlling), the dosing frequency (once weekly, QD, BID or TID), sex, coping (avoidance, passive reaction pattern, and expression of emotions), and the overall health (total NHP score) together explained 66.6% of the variance in taking compliance (adjusted R^2) (p = 0.002; Table 4). In this regression model there was little colinearity between the variables, and the residual error was randomly distributed, indicating good fit of the model. The result for correct dosing was roughly equal (adjusted R^2 = 52%, p = 0.014, with the standardized ß-coefficient for sex being statistically not significant. For timing compliance the model did not converge, probably due to the strongly skewed distribution of the timing compliance variable, as shown in Figure 4.

Table 4. Predictors of "taking" compliance: a multiple regression model with backward removal of variables.

Variable in the Regression Equation	Standardized ß	Unstandardized ß
Constant		65.4
Class of medication (symptom modifying or disease controlling)	–0.66	–23.3
Dosing frequency	1.16	8.2
Sex	0.38	13.5
Partial R^2	0.31	
Coping		
Avoidance	–0.41	–2.2
Passive reaction pattern	0.79	5.0
Expression of emotions	0.40	3.5
NHP	–0.62	–1.7
Partial R^2	0.36	
Total R^2	0.67	

All ßs: p < 0.05.
Independent variable: taking compliance.
Class of medication: 1 = symptom modifying, 2 = disease controlling, 3 = both.
Dosing frequency: 1 = once daily, 2 = twice daily, 3 = thrice daily, 7 = once-weekly.
Gender: 0 = female, 1 = male.
Coping: Avoidance (7 = lowest, 56 = highest), passive reaction pattern (7 = lowest, 32 = highest), expression of emotions (3 = lowest, 19 = highest).
NHP: 0 = lowest, 34 = highest

DISCUSSION

The use of electronic monitors to investigate patient compliance is relatively new in rheumatology. While the method is indirect, in that it does not prove ingestion, it nevertheless captures, with indelible time stamping, the occurrence of the maneuvers needed to remove a dose of drug from the monitored drug package. In this respect electronic medication event monitoring differs sharply with other methods for estimating patient compliance, such as returned pill counts, patient reports, questionnaires, diaries, and physician estimates, each of which can be altered at any time by one or a few simple acts (such as emptying the pillbox, or exaggerating compliance on a questionnaire, or a "little white lie" when asked for the number of tablets taken)[27]. With electronic monitoring, the clock cannot be reset, so that a dose not taken remains a dose not recorded. In addition, electronic monitoring is automatic, does not rely on memory, and is noninvasive. All this means that the use of electronic monitoring offers several advantages in both accuracy and precision of measurement, providing better data than the more traditional methods.

The patients were aware of how the monitoring took place. A few patients complained at the end of the study that they had felt like they were being watched, which in turn had increased their compliance. There were no instances in which patients reported having taken less medicine because of the monitors. Indeed, there were a number of patients who had forgotten about the monitoring nature of the package when they were contacted to return the monitor.

This study reports the first data on electronically compiled dosing histories in a diverse population of patients with rheumatic conditions. Thus, it provides an unprecedented look into patients' compliance behavior, revealing some very clear and relevant differences between diseases, between drugs, and most of all between patients.

Compliance with DMARD and prednisone was in general much better than compliance with NSAID and antigout therapy. However, compliance with SSZ, prescribed BID, appeared to be substantially and significantly lower than compliance with once-weekly MTX. Compliance with prednisolone in PMR was very good, with very little interpatient variability, meaning not just that the average was high, but that indeed almost all patients prescribed prednisone were taking the medication in very close correspondence to the prescribed regimen. Compliance with NSAID in RA and uric acid lowering agents in gout was clearly low, even though the medication was prescribed to be taken daily, not "on demand," although the latter more closely resembles the way that most of the patients actually took these agents. The level of compliance with NSAID that we observed was strikingly similar to the compliance with once-daily prescribed piroxicam and tenoxicam that we investigated, using the same method, for patients with ankylosing spondylitis[3]. Compliance taking colchicine maintenance therapy was, perhaps not unexpectedly, lowest of all.

Transformation of the dosing histories to a summary variable is an important issue, because summarization of temporal patterns inevitably results in loss of precision[28]. The dosing histories per se, as depicted in Figure 2, cannot be analyzed without some sort of summarization. We chose to report 3 different compliance variables: taking compliance, correct dosing, and timing compliance. Each represents different aspects of dose taking. Taking compliance provides a gross estimate of all doses taken over a long period. This variable is insensitive to dosing errors (such as taking a dose late or catch-up dosing, where a missed dose is followed by a day with, for example, 2 doses). It thus provides mainly insight into overall drug exposure over the monitored period. It resembles the traditional pill count, but with the difference that for each "pill" to be counted, the monitor has to be opened and closed, and with automatic time stamping.

Correct dosing, where the percentage of days with the correct number of doses is summarized, reflects more the intention of the patient to take the medication as prescribed. It does not correct for catch-up dosing, but variations within interdose-intervals are allowed. Timing compliance focuses on these interdose-intervals, and is the strictest of the 3. The differences in length of interdose-intervals (8 hours for TID and 168 hours for once-weekly) were corrected for by giving a relative leeway of ± 25% of the interdose-intervals rather than absolutely defined intervals.

We clearly see differences in taking compliance (which in general is highest), correct dosing, and timing compliance (which is lowest). Indeed, as can be seen in Figure 3c, timing compliance is very low for most drugs except MTX in RA and prednisolone in PMR, perhaps providing insight into tactics to follow in compliance interventions.

Less frequent dosing was strongly related to better compliance. This relationship has been observed with electronic medication event monitoring in other fields of medicine[29]. Interestingly, once-weekly dosing is associated with better compliance than more frequently dosed SSZ. Recently, 4 other studies, utilizing electronic monitoring with once-weekly prescribed drugs, showed the same superior compliance[30-33]. As once-weekly MTX is readily available in rheumatology, we regard this as a very interesting finding that warrants further research.

The relationship between the individual demographic and questionnaire variables and compliance was weak. In particular, the lack of a relationship between compliance and side effects may come as a surprise. However, it is clear that such a relationship is by no means simple. The early onset of severe side effects may result in discontinuation of the drug, while less severe, noticeable side effects may actually be perceived as "the drug is working." Another interpretation of the lack of the relationship may be that the questionnaire to capture information about side effects systematically in this study is not the optimal way to do so. In particular, the way the data from the questionnaire are transformed to a variable that is related to

compliance may not be optimal. Due to the heterogeneity of the patient sample and the lack of a gold standard for side effects the lack of relationship between compliance and side effects needs to be interpreted with caution.

However, combining the variables in a multiple regression analysis showed that combination of a few variables predicts taking compliance and correct dosing to a substantial degree. The key variables are the nature of the drug (symptom modifying associated with lower compliance than disease controlling, while systemic steroids, dual properties, are associated with the highest compliance); the dosing regimen (less frequent dosing results in higher compliance); sex (females show higher compliance); coping (avoidance is related with lower compliance, expression of emotions and passive reaction pattern are related with higher compliance); and overall perceived health (where higher perceived health is related with lower compliance). The overall correlation of this multiple regression correlation with taking compliance, adjusted for multiple variables in the equation, was high (adjusted R^2 = 0.67). Closer examination of the model shows that the variables that are fixed (nature of drug, dosing regimen, and sex) explain a total of 45.8% of the explained variance, while the other variables (the 3 coping variables avoidance, passive reaction pattern, and expression of emotions, and the overall perceived health) explain a total of 54.2% of the explained variance. Given the relatively small size of the study and the very heterogeneous study population we await confirmation of the model in other studies; however, if these variables do appear to be statistically significantly related to taking compliance and correct dosing, they might provide an important clinical tool for compliance awareness and perhaps compliance intervention.

Studying patient compliance with prescribed drug regimens utilizing electronic medication event monitors in RA, gout, and PMR showed that large differences exist in compliance between the various medication groups. Compliance declines over time. A regression model shows that it is possible to relate differences in patient compliance to a number of medication and patient related factors.

ACKNOWLEDGMENT

We acknowledge the assistance of the AV dienst of the Maastricht University Hospital, who kindly helped with the inclusion of patients in this study.

REFERENCES

1. Hasford J. Biometric issues in measuring and analyzing practical compliance in clinical trials. In: Cramer JA, Spilker B, editors. Patient compliance in medical practice and clinical trials. New York: Raven Press; 1991:265-82.
2. Urquhart J. Patient compliance with prescribed drug regimens: overview of the past 30 years of research. In: Nimmo WS, Tucker CT, editors. Clinical measurement in drug evaluation. New York: John Wiley & Sons; 1995:213-27.
3. de Klerk E, van der Linden SJ. Compliance monitoring of NSAID drug therapy in ankylosing spondylitis, experiences with an electronic monitoring device. Br J Rheumatol 1996;35:60-5.
4. Urquhart J, De Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. Stat Med 1998;17:251-67.
5. de Klerk E. Measurement of patient compliance on drug therapy. In: Vingerhoets A, editor. Advances in behavioral medicine assessment. City: publisher; 1998:pages.
6. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. Drugs 1995; 49:321-7.
7. Kastrissios H, Blaschke TF. Medication compliance as a feature in drug development. Annu Rev Pharmacol Toxicol;37:451-75.
8. Urquhart J. The electronic medication event monitor — lessons for pharmacotherapy. Clin Pharmacokinet 1997;32:345-56.
9. Farmer K. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999;21:1074-90.
10. Arnet I, Haefeli W. Overconsumption detected by electronic drug monitoring requires subtle interpretation. Clin Pharmacol Ther 2000;67:44-7.
11. George C, Peveler R. Compliance with tricyclic antidepressants. Br J Clin Pharmacol 2000;50:166-71.
12. Liu H, Golin C, Miller L, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001;134:968-77.
13. Strom B. Pharmacoepidemiology: Wiley; Chichester: 1994:741.
14. van der Heijde D, van Riel P, van de Putte L. Sensitivity of a Dutch Health Assessment Questionnaire in a trial comparing hydroxychloroquine vs sulphasalazine. Scand J Rheumatol 1990;19:407-12.
15. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Pract 1985;35:185-8.
16. Schreurs PJG, van de Willige G, Brosschot JF, Tellegen B, Graus GMH. De Utrechts coping lijst: UCL, herziene handleiding. Utrecht: Vakgroep Klinische Psychologie en Gezondheidswetenschappen; 1993.
17. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.
18. De Geest S, Abraham I, Gemoets H, Evers G. Development of the long-term medication behaviour self-efficacy scale: qualitative study for item development. J Adv Nurs 1994;19:233-8.
19. Tijhuis G, de Jong Z, Zwinderman A, et al. The validity of the Rheumatoid Arthritis Quality of Life (RAQol) questionnaire. Rheumatology 2001;40:1112-9.
20. de Jong Z, van der Heijde D, McKenna SP, Whalley D. The reliability and construct validity of the RAQol: a rheumatoid arthritis-specific quality of life instrument. Br J Rheumatol 1997;36:878-83.
21. Whalley D, McKenna SP, de Jong Z, van der Heijde D. Quality of life in rheumatoid arthritis. Br J Rheumatol 1997;36:884-8.
22. de Geest S, Borgermans L, Gemoets H, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995;59:340-7.
23. Physicians desk reference. Montval, NJ: Medical Economics Co.; 1997.
24. Lesaffre E, de Klerk E. Estimating the power of compliance-improving methods. Control Clin Trials 2000;21:540-51.
25. Urquhart J, Chevalley C. Impact of unrecognized dosing errors on the cost and effectiveness of pharmaceuticals. Drug Information Journal 1988;22:363-78.
26. de Klerk E, van der Linden S, van der Heijde D, Urquhart J. Facilitated analysis of data on drug regimen compliance. Stat Med 1997;16:1653-64.
27. de Klerk E. Measurement of patient compliance with drug therapy.

In: Vingerhoets A, editor. Assessment in Behavioral Medicine. New York: Brunner-Routledge; 2001:215-43.
28. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. Control Clin Trials 1997;18:187-203.
29. Claxton A, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296-310.
30. Ridwan E, Schultnik W, Dillon D, Gross R. Effects of weekly iron supplementation on pregnant Indonesian woman are similar to those of daily supplementation. Am J Clin Nutr 1996;63:884-90.
31. Galloway R, McGuire J. Daily versus weekly: how many pills do pregnant woman need? Nutr Rev 1996;54:318-23.
32. Iorillo D, Landry P, Darioli R. Electronic monitoring of travellers' adherence to mefloquine malaria chemoprophylaxis. Poster presented at 6th Conference of the International Society for Travel Medicine, Montreal, Quebec, 1999.
33. Claxton A, de Klerk E, Parry M, Robinson J, Schmidt M. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. J Clin Psychiatry 2000;61:928-32.