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Patient Compliance in Rheumatoid Arthritis, Polymyalgia Rheumatica, and Gout

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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
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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 <

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	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).

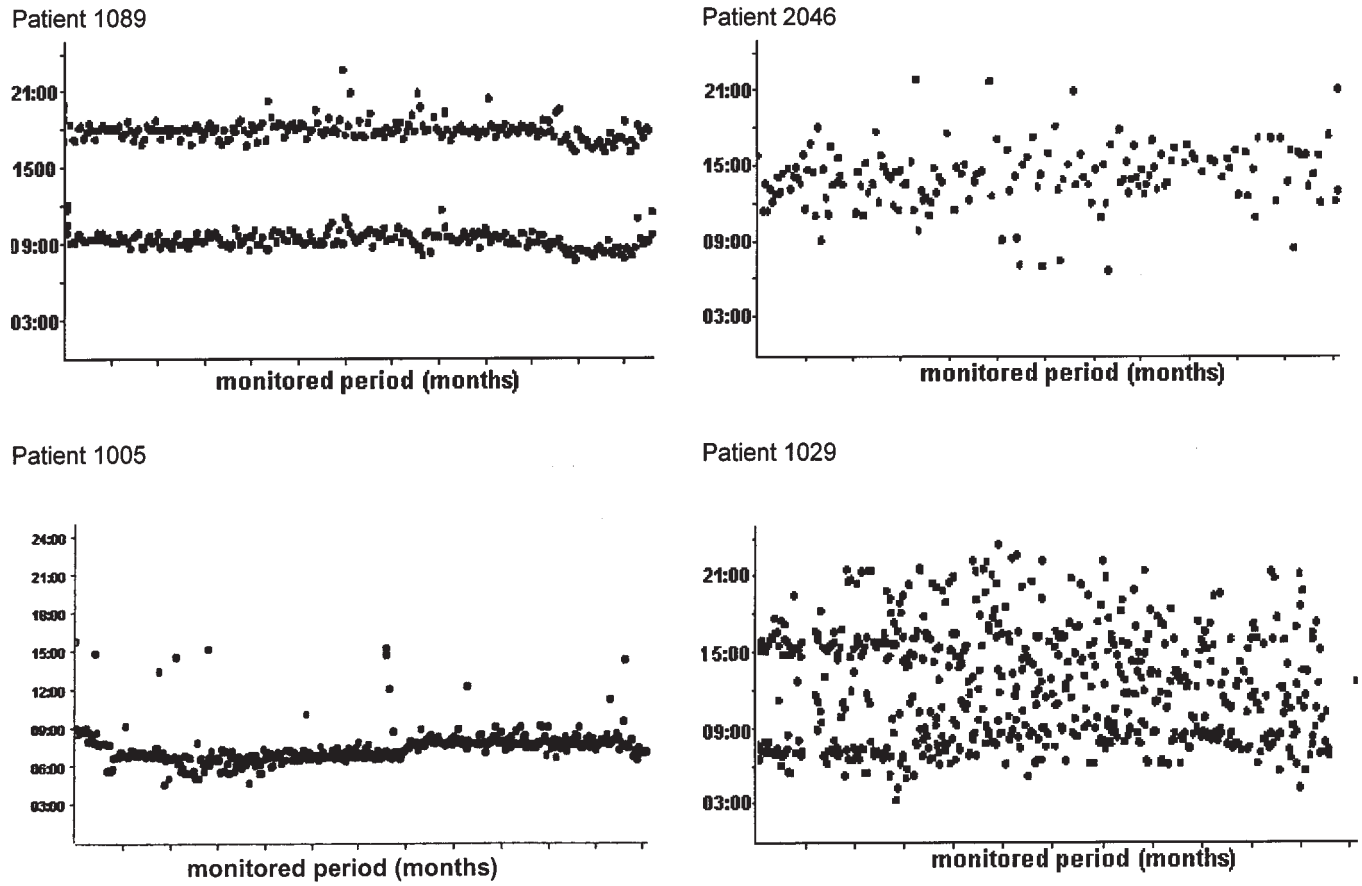

Figure 2. Example of 4 chronology plots. Patient 1089 is a patient with RA taking BID SSZ. She is taking almost 100% of the drugs, but is taking the doses in relatively short intervals, resulting in a lower timing compliance (25%). Patient 2046 is a gout patient taking QD allopurinol (see Figure 1), 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%.

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