Peer reviewed article

Monitoring adherence to prescribed medication in type 2 diabetic patients treated with sulfonylureas

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Summary

Background: Data on adherence to prescribed medication amongst diabetics are scarce. The purpose of this study was to collect information about the dynamics and patterns of compliance of elderly patients with type 2 diabetes mellitus on oral treatment by using different assessment techniques.

Methods: Adherence to prescribed sulfonylurea medication was prospectively assessed by Self-report (Sr), Pill count (Pc) and using a Medication Event Monitoring System (MEMS) over a period of 2 months in 19 elderly patients with type 2 diabetes mellitus. A pressure-activated microprocessor allowing the registration of each opening is located in the cap of the MEMS drug container. MEMS dosage adherence ($MEMS_d$) was defined as the number of bottle openings divided by the number of doses prescribed), and MEMS regimen adherence ($MEMS_r$) was defined as the percentage of days in which the dose regimen was taken as prescribed.

Results: Adherence rates were 96.8 ± 19.6% for Pc, 92.6 ± 19.9% for $MEMS_d$ and 78.6 ± 28.3% for $MEMS_r$. Adherence rates for Pc were 103.8 ± 10.9% in once daily regimens and 87.3 ± 25.2% in bid/tid regimens (p = 0.0686). $MEMS_d$ was 101.0 ± 4.8% in once daily regimens versus 81.0% ± 26.8% in bid/tid regimens (p = 0.0255). $MEMS_r$ was 93.6 ± 5.7% in once daily regimens versus only 57.8 ± 34.1% in bid/tid regimens (p = 0.0031). Assessed by $MEMS_d$ as many as 42.1% of the participants had adherence rates greater than 100%. Over-compliance was found primarily in once daily regimens.

Conclusion: Adherence rates varied with different assessment techniques. Adherence rates were far from optimal. Once daily dosage led to significantly better adherence rates than two or three times daily regimens. However, over-compliance was surprisingly high and occurred more frequently on a once daily regimen.

Key words: type 2 diabetes mellitus; oral hypoglycaemic medication; adherence; compliance

Introduction

Patients often do not take their medication as prescribed, and the reasons for non-adherence to prescribed medication are very heterogeneous [1]. Non-adherence will reduce the efficacy of the medication [2] and may lead to additional diagnostic procedures or treatments [3, 4]. In addition, it has been demonstrated that non-adherence contributes to unnecessary hospital admissions [5]. To quantify non-adherence assessment techniques such as self-report, pill count and serum drug concentrations have been used. However, all these methods tend to overestimate adherence [6]. Self-reports are biased due to incomplete recollection, self-delusion or the wish to please the physician. Pill counting is often delicate. Even if the number of remaining tablets may suggest excellent adherence, it remains unclear to what degree missed doses have been balanced with other extra pills [7]. In addition, it is not possible to obtain information about the patterns of intake such as intervals between two doses, which can be important with respect to the serum steady state level of the drug. Some patients may even remove remaining pills just before seeing their physician [8]. To improve assessments of adherence different approaches have been introduced to monitor pill consumption by means of electronic devices. Among these methods the so called Medication Event Monitoring System (MEMS), a pressure-activated bottle with a monitor concealed in the cap has become more widely used [7]. All these methods are based on the assumption that each opening of the container actually corresponds to the patient consuming medication.

Factors predisposing for low adherence rates are chronic disease, delayed consequences of stop-

This work was partially supported by a grant from Aventis AG (Zürich, Switzerland).

ping medication, advanced age, ambulatory treatment, and complicated drug regimens [9]. These factors all apply to patients with type 2 diabetes mellitus on oral hypoglycaemic agents who might therefore be expected to adhere particularly badly to their treatment. On the other hand diabetics are reminded of their disease (and therefore possibly of the necessity of its treatment) with each meal and for many diabetics taking medication might be easier to adhere to, than following a diet or doing exercise [10]. So far, few studies have assessed adherence to prescribed oral hypoglycaemic medication in type 2 diabetes mellitus [11–14]. The reported adherence rates vary between roughly 30% to 80%. The present study was conducted to get more information on adherence rates and in particular on patterns of adherence to prescribed sulfonylurea medication in patients with type 2 diabetes mellitus; and to compare Sr, Pc and MEMS as means of assessing adherence. The investigation was not designed to change or improve adherence, since patterns of non-adherence had to be understood first.

Patients and methods

Patients

Adherence to prescribed sulfonylurea medication was monitored prospectively over a period of approximately 2 months in 19 patients (13 men, 6 women) with type 2 diabetes mellitus. They were treated with glibenclamide or glimepiride without concurrent insulin medication. All patients lived independently and administered their medication themselves. The dosage of the sulfonylurea regimen remained unchanged during the period of investigation. The mean age was 68.8 ± 10.7 years (mean ± SD, range: 49 to 83) with a diabetes duration of 12.2 ± 9.3 years (range: 1 to 38). The mean HbA_{1c} (measured by DCA 2000™ [Bayer AG, Zürich, Switzerland], normal range: 4.1–5.7% [mean – 2SD to mean + 2SD]) was 7.9 ± 1.7% (range: 5.4 to 12.5). During the study HbA_{1c} increased slightly by 0.4 ± 0.7% (n.s.).

Study design

Patients volunteered to participate in the study following a written invitation posted in our outpatient clinics. The indicated study purpose was the evaluation of different package materials for sulfonylureas. The patients had two appointments at our outpatient clinic. At the first visit they were told that the purpose of the study was to compare a "new" container (which in fact was a Medication Event Monitoring System [MEMS] with a pressure-activated microprocessor concealed in the cap) with the standard blister packs which they had used so far. A sufficiently large, counted number of sulfonylurea tablets was filled into MEMS before delivery to the patient. If patients took any concomitant drugs they were told to continue this medication as usual. Thus, apart from introducing a MEMS, the medication setting remained unchanged. In order to reduce potential influence on behaviour of patients and to minimise bias introduced by the process of an ongoing study, patients were deliberately not informed of the real study purpose and the monitoring, and strictly no allusions referring to compliance were made. The second visit was scheduled after an interval typical for each individual patient (i.e., after 54 ± 8 days). At the follow-up visit the patients were asked additional questions about their medication and diet habits (self-report) during the study period and pill counting was performed. Finally, the real purpose of the study was revealed to patients and they were informed that their adherence to prescribed medication had been monitored. Before retrieving the data from the microprocessor, written, informed consent was obtained. Blood was taken at both visits for measurements of fasting blood glucose and HbA_{1c}. This study procedure was developed in accordance with and approved by the ethics committee of the medical faculty of the University of Bern.

Assessment of adherence

Self-report (Sr): Patients were asked to describe their medication behaviour during the last eight weeks answering the following questions: 'Did you ever forget to take your medication?', 'Did you ever take your medication at the wrong time?', 'Did you ever take additional doses?'. Furthermore, patients had to rate their adherence to pill-taking and to their diet on a visual analogue-scale ranging from 1 to 9.

Pill count (Pc): Pc was conducted when the patients returned their bottle. Initially, more tablets were put into the container than actually needed, so that over-consumption (over-adherence) could also be detected. Adherence assessed with Pc was defined as the number of tablets removed from the container divided by the number of tablets prescribed (expressed in %).

Medication Event Monitoring System (MEMS, Aardex Ltd., Zug, Switzerland): This system uses a pressure-activated microprocessor concealed in the cap of the bottle. Each opening was recorded precisely, which means that date, exact time, duration and elapsed time since the previous opening were listed. Multiple openings within a particular time period (15 min) were filtered and not counted, all other openings were regarded as a presumptive dose. Data were retrieved from the MEMS monitor by connecting to a microcomputer communication port. MEMS dosage adherence (MEMSd) was defined as the number of bottle openings divided by the number of doses prescribed (expressed in %). As dosage adherence does not take into account the timing of the dose removal, regimen adherence (MEMSr), which quantifies daily adherence, was also assessed. MEMSr was defined as the percentage of days in which the dose regimen was taken as prescribed (expressed in %).

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical analysis included Fisher's Exact Test for proportions and Student's t-test for differences. Correlation coefficients, partial correlation coefficients and squared multiple correlation coefficients were used to assess interdependencies between variables. Two-tailed p values <0.05 were considered statistically significant.

Results

A total of 1032 days were monitored with a mean duration of 54 ± 8 days per patient. 1290 openings were recorded whereas 1499 were expected (86.0% of the prescribed doses). The mean adherence rates as well as the individual adherence rates are summarised in table 1. Pc data yielded an adherence rate of 96.8 ± 19.6% (range: 34.7–132.7%), with seven patients taking more tablets than prescribed. Three patients returned the exact number of pills (100% adherence). $MEMS_d$ (number of bottle openings divided by prescribed openings in percent) was 92.6 ± 19.9% (range: 34.5–111.0%), with eight patients opening the bottle more often than prescribed. $MEMS_r$ (number of days with correct openings in percent) was 78.6 ± 28.3% (range: 11.2–100.0%). The mean value given for Sr on medication accuracy was 8.3 ± 1.2 (with 9 being the best value on a visual analogue-scale ranging from 1 to 9), whereas Sr concerning diet yielded a mean score of 6.9 ± 2.0 (on the same scale). Correlations between the different measurements of adherence are shown in table 2. Pc data correlated significantly with $MEMS_d$ ($r = 0.560$, $p = 0.0114$). $MEMS_d$ correlated well with Sr adherence rates concerning diet ($r = 0.637$, $p = 0.0026$), but it did not correlate significantly with Sr adherence rates concerning tablet intake ($r = 0.367$, $p = 0.1231$). The best correlation was found between $MEMS_d$ and $MEMS_r$ ($r = 0.864$, $p < 0.0001$). A very weak partial correlation coefficient was found between Pc and $MEMS_r$ ($r_{partial} = 0.096$), indicating that a combination of these two parameters could be especially helpful in identifying non-compliers.

To assign patients to categories the "compliant" and "non-compliant", a definition proposed by other authors [15, 16], was applied: If the patient achieved an adherence rate of >90% he was considered compliant. Assessed by Pc as well as by $MEMS_d$, 15 patients (78.9%) were compliant (table 3). Assessed by $MEMS_r$ on the other hand, only nine patients (47.4%) were compliant. Of the ten patients identified as non-compliant by $MEMS_r$, five (26.3%) would have been misclassified as compliant if only Pc or $MEMS_d$ had been considered. Pill counting detected 40%, $MEMS_d$ 40% and $MEMS_r$ detected 100% of non-compliers identified by one or more methods. Combining Pc and $MEMS_d$ 50% of non-compliers were detected.

Eight patients (42.1%) had an adherence rate of >100% assessed by $MEMS_d$. Over-adherence with sulfonylureas can lead to serious side effects (hypoglycaemia). Therefore, as an alternative, an upper limit for adherence was also set, and adherence rates of 90–110% were considered compliant.

Table 1

Individual adherence assessments (Sr = Self report; Pc = Pill count; MEMS = Medication Event Monitoring System).

Patient No.	Dosage	Sr: diet [a]	Sr: medication [b]	Pc (%)		MEMS dosage adherence (%)		MEMS: regimen adherence (%)	
1	1	6	8	101.4		101.4		98.6	
2	1	9	8	100.0		101.8		83.9	nc
3	1	7	9	110.5	nc↑	94.7		84.2	nc
4	1	5	9	132.7	nc↑	102.0		98.0	
5	1	9	9	96.4		103.6		94.6	
6	1	9	9	104.8		109.5		90.5	
7	1	7	9	93.3		97.8		93.4	
8	1	9	9	94.6		94.6		94.6	
9	1	9	9	107.9		107.9		92.1	
10	1	5	9	100.0		98.2		100.0	
11	1	8	9	100.0		100.0		100.0	
12	2	9	9	95.5		93.2		88.9	nc
13	2	5	7.5	87.1	nc↓	87.1	nc↓	76.0	nc
14	2	9	9	95.2		111.0	nc↑	89.3	nc
15	2	6	7	115.2	nc↑	100.0		89.0	nc
16	2	5	8	34.7	nc↓	34.5	nc↓	28.1	nc
17	2	5.5	5.55	71.3	nc↓	102.0		64.7	nc
18	2	2.5	5	110.3	nc↑	52.4	nc↓	11.2	nc
19	3	5	9	89.1	nc↓	68.0	nc↓	15.5	nc
mean		6.9	8.3	96.8		92.6		78.6	
SD		(2.0)	(1.2)	(19.6)		(19.9)		(28.3)	

[a] + [b] rated on a visual analogue-scale with 9 being very accurate to 1 being inaccurate
nc non compliant
nc↑ non compliant (over-consumption)
nc↓ non compliant (under consumption)

Table 2

Correlation between different parameters of adherence to prescribed sulfonylurea medication. Correlation coefficients are shown off diagonals, and squared multiple correlation coefficients (in bold) are shown in diagonals.

	Sr diet (%)	Sr medication (%)	Pc (%)	$MEMS_d$ (%)	$MEMS_r$ (%)
Sr diet	**0.658**				
Sr medication	0.622**	**0.503**			
Pc	0.105	0.157	**0.447**		
$MEMS_d$	0.637**	0.367	0.560*	**0.842**	
$MEMS_r$	0.635**	0.521*	0.443	0.864***	**0.796**

p-values: * p <0.05; ** p <0.001; *** p <0.0001

Table 3

Proportion of compliers using different methods to measure (Pc, $MEMS_d$, $MEMS_r$) and define (A: adherence rate >90%; B: adherence rate 90–110%) adherence. Comparison between patients on a once daily vs. a twice (bid) or three times daily (tid) regimen.

	>90%			90–110%		
	Pc	MEMS dosage	MEMS regimen	Pc	MEMS dosage	MEMS regimen
overall	15 (78.9%)	15 (78.9%)	9 (47.4%)	11 (57.9%)	14 (73.7%)	9 (47.4%)
once daily	11 (100%)	11 (100%)	9 (81.8%)	9 (81.8%)	11 (100%)	9 (81.8%)
bid/tid	4 (50%)	4 (50%)	0 (0%)	2 (25%)	3 (37.5%)	0 (0%)
p	0.0181	0.0181	0.0007	0.0237	0.0048	0.0007

Assessed in this fashion Pc, $MEMS_d$ and $MEMS_r$ revealed that 57.9, 73.7 and 47.4% of the patients respectively could be considered compliant (see table 3). Using this alternative definition of adherence Pc, $MEMS_d$ and $MEMS_r$ detected 72.7, 45.5 and 90.9% of non-compliers respectively. Only the combination of Pc and $MEMS_r$ detected all non-compliers. Combining Pc, and $MEMS_r$ only 42.1% of the patients were considered compliant (adherence rates of 90–110%).

Adherence assessed by Pc was 103.8 ± 10.9% and 87.3 ± 25.2% for the patients on the once daily and bid/tid regimens, respectively; the difference is not quite significant (p = 0.0686). The $MEMS_d$ adherence rate was 101.0 ± 4.8% with the once daily regimen and 81.0% ± 26.8% with the bid/tid regimen (p = 0.0255). The $MEMS_r$ adherence rate with the once daily regimen was 93.6 ± 5.7% compared to 57.8 ± 34.1% with the bid/tid regimen (p = 0.0031). All of the patients on a once daily regimen were compliant assessed by Pc as well as by $MEMS_d$ according to the definition of >90%, whereas only half of the bid/tid regimen group was compliant (p = 0.0181; see table 3). $MEMS_r$ adherence classified 9 patients out of 11 (81.8%) on the once daily regimen as compliant and none of the bid/tid group (p = 0.0007). In addition, over-adherence occurred more often in the once daily group (54.5% had a adherence rate of >100% in the once daily vs. 25% in the bid/tid group assessed by $MEMS_d$). Using the alternative definition for adherence of 90–110%, Pc adherence rate was 81.8% for the once daily regimen vs. 25% for the bid/tid regimen (p = 0.0237), and $MEMS_d$ adherence rate was 100% for the once daily regimen vs. 37.5% for the bid/tid regimen group (p = 0.0048). Monitoring $MEMS_r$, the following rates were obtained: 81.8% of the once daily regimen and none of the bid/tid group could be considered compliant (p = 0.0007).

Discussion

Assessment of adherence to prescribed medication is difficult. Recently, the use of MEMS and similar devices has become a helpful assessment method. Using this method we found comparatively high adherence rates ($MEMS_d$: 92.6 ± 19.9%, $MEMS_r$: 78.6 ± 28.3%) in patients with type 2 diabetes mellitus on treatment with oral hypoglycaemic agents. Adherence rates were significantly better in patients on once daily vs. twice or three times daily regimens. In addition, over-adherence (assessed by $MEMS_d$) was comparatively frequent and was found in 42.1%. The sensitivity to detect non-compliers identified by one or more methods varied considerably, and Pc, $MEMS_d$ and $MEMS_r$ detected 72.7, 45.5 and 90.9% of non-compliers respectively. Only the combination of Pc and $MEMS_r$ was able to detect all non-compliers.

Two other studies have assessed adherence rates in patients with type 2 diabetes mellitus using MEMS [11, 12]. Paes et al. [11] found lower adherence rates than we did, with $MEMS_d$ and $MEMS_r$ adherence rates of 74.8% and 67.2% respectively. Adherence rates were better in patients on a once daily regimen compared to those on a twice or three times daily regimen. Unfortunately, in this study the patients were poorly characterised. For two patients even the gender was unknown [11b]. In addition, it is unclear to what degree the patients were informed on the purpose of the study. The study was not approved by an

ethics committee and it appeared as a double publication [11a, 11b]. The second trial by Mason et al. [12] investigated patients in poor or fair metabolic control. In this study patients were aware of the fact that medication taking behaviour was assessed. Surprisingly, in 11 out of 32 patients, all methods of assessment (interviews, self-assessment, pill count and MEMS data) showed no qualitative and quantitative difference in adherence rates. 53% of the patients were classified as adherent (defined as having an adherence rate of 90–105%, assessed by $MEMS_r$). Recently, two large, retrospective studies based on databases on pharmacy claims [13] or prescriptions [14] have been reported. In more than 52 000 patients on sulfonylurea medication Boccuzzi et al. [13] determined an average adherence rate of 80.1%. Due to the fact that their adherence indices were not normally distributed Dannon et al. [14] do not report numeric mean values. However, from graphical demonstration of adherence indices the mean value can be estimated to be somewhere between 70 and 80%. Our own average adherence rates are higher than the ones reported in these studies [11–14], which is not really surprising since our patients where recruited from the outpatient clinics at a specialised centre and possibly represent more motivated patients than average. In addition, the high rate of over-adherence found in our study is balancing out under-adherence, and thus leads to higher average adherence rates. Differences in the reported adherence rates may reflect methodological differences, differences in study populations selected or real differences between ethnically and geographically distinct populations of type 2 diabetics. Despite differences reported, even in our own study combining Pc, and $MEMS_r$ only 42.1% of the patients were considered compliant (adherence rates of 90–110%).

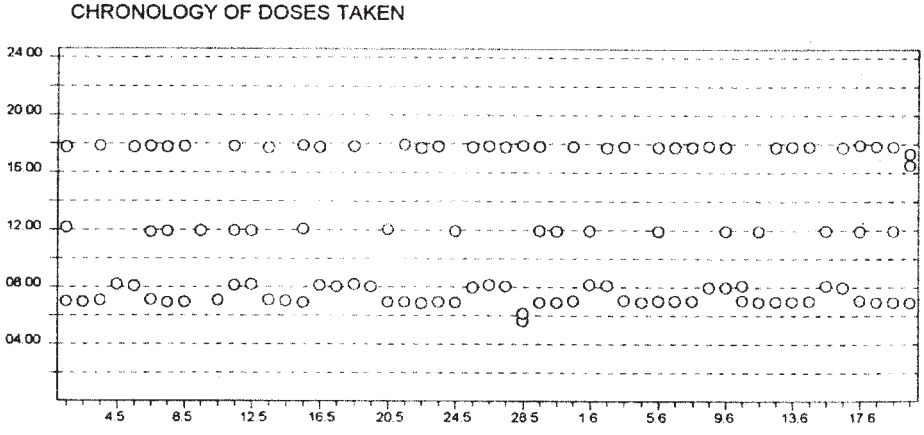
Concerning the influence of daily dosage on adherence, Eisen et al. who investigated adherence to antihypertensive medication by means of MEMS observed similar results [17]. Adherence on a once daily regimen was not significantly different from adherence on a twice daily regimen. However, patients on a three times daily regimen did get lower adherence rates in their study. Pullar et al. also reported that adherence rates on a once or twice daily regimen were very similar. In this study added phenobarbital with consecutive serum measurements served as an indicator of adherence [18]. Studying patients on oral chemotherapy Lee et al. showed a reduction in overall adherence as the number of prescribed doses increased from one to two [19]. In our study, the difference of adherence rates between once daily and twice or three times daily regimen was statistically significant assessed by $MEMS_d$ as well as $MEMS_r$. This is clearly supported by the studies of both Paes et al. [11] and Donnan et al. [13].

As an interesting new finding we determined that over-adherence was surprisingly frequent with a $MEMS_d$ adherence rate higher than 100% in 42.1% of the patients. In some situations over-adherence may be uncritical, in other situations it may lead to serious hypoglycaemia. Interestingly, over-adherence occurred more often in the group on a once daily regimen. Several publications exist on adherence to prescribed medication in other chronic diseases using MEMS [6, 7, 20, 21]. However, these studies as well as the studies by Paes et al. [11] and Mason et al. [12] did not find over-adherence. Dannon et al. do not directly report over-adherence, but from their graphical illustration of adherence indices it can be presumed that a relevant proportion of their study population actually demonstrated over-adherence, since their drug coverage was greater than 365 days per year.

Not surprisingly, in our study Pc and $MEMS_d$ adherence rates correlate quite well, since they both reflect the number of tablets removed. $MEMS_d$ and $MEMS_r$ adherence rates also show a high correlation, but $MEMS_r$ adherence rates reveal additional information giving insight into the dynamics of intake. Interestingly, the $MEMS_d$ adherence rate correlated significantly with Sr diet but not with Sr tablets. It seems that the patients more readily realise and/or admit inaccuracies concerning diet than concerning intake of prescribed medication. A closer look at the patterns of adherence in some specific patients is informative. The Pc and $MEMS_d$ data for *patient No.2* both suggested a compliant behaviour. However, when looking at $MEMS_r$, non-compliance is detected. In

Figure 1

Chronology of doses taken (example of patient No. 17).



addition, the detailed printout revealed a particular repetitive pattern. On four Fridays the patient took two doses instead of one and none the following morning. The second opening always happened late at night, when the participant spent the night out and took an additional dose before going to bed. This example illustrates how balanced non-adherence can only be detected by modern techniques. *Patient No.17* had a $MEMS_d$ adherence rate that was much higher than the Pc adherence rate (102.0% vs. 71.3%). He was on a bid regimen. The chronology of doses taken (figure 1) shows additional events mainly around noon. Checking with the patient revealed that he sometimes did split up the morning dose, which consisted of 2 tablets, and took the second tablet at noon. However, the $MEMS_d$ adherence rate should have been much higher if this were the only change the patient made. The calendar plot reveals that on many days he only took one dose. That is why the overall $MEMS_d$ adherence rate was balanced and finally led to an apparently good result whereas the $MEMS_r$ adherence rate did reveal non-compliance. This example shows that the different assessment methods should be used in a complementary way. Comparing all techniques, including electronic data, helps best to understand a specific pattern of non-compliance. The combination Pc and $MEMS_r$ seems particularly helpful.

Our study has several weaknesses: (1) The assumption on which the use of the MEMS is based, namely that a bottle opening corresponds to a tablet ingestion is, of course, a simplification. A patient can obviously open the device without removing a tablet. However, openings within less than 15 minutes were filtered out and thus not counted. It is most unlikely that the remaining openings are the result of the patient opening this device each day over a prolonged period without taking the medication. In addition, this form of non-compliance should have been detected by pill counting. (2) Apart from the relatively small sample size, which of course could be misleading, (3) a selection bias could have been introduced if the population participating in such studies differed from the normal population. This is not unlikely since participants in any studies are possibly highly motivated. (4) The attention of participants could be focused unintentionally on medication during the study, even if no information about the purpose of the study was given. With our study design we have tried to minimise the importance of some of these problems. The facts that adherence rates ($MEMS_d$ and $MEMS_r$) as well as HbA_{1c} did not change during the study are indications that bias introduced by the process of an ongoing study was comparatively unimportant. Compared to the named weaknesses inherent to the method, an apparent strength of our study is the fact, that patients were completely unaware of the monitoring, which was not the case in previous studies performed in diabetic subjects. This allowed detection of specific patterns of adherence as shown in the illustrated case.

In conclusion, our study shows that adherence rates in type 2 diabetics (assessed by Pc, $MEMS_d$ as well as $MEMS_r$) are far from optimal. The best information about adherence to prescribed medication and its dynamics is provided by comparing different assessment techniques in a complementary way. In particular $MEMS_r$ provides complimentary information regarding patterns of non-adherence. Importantly, we found significantly better adherence rates in patients on a once daily regimen compared to those on a twice or three times daily regimen. In addition, over-adherence was surprisingly high.

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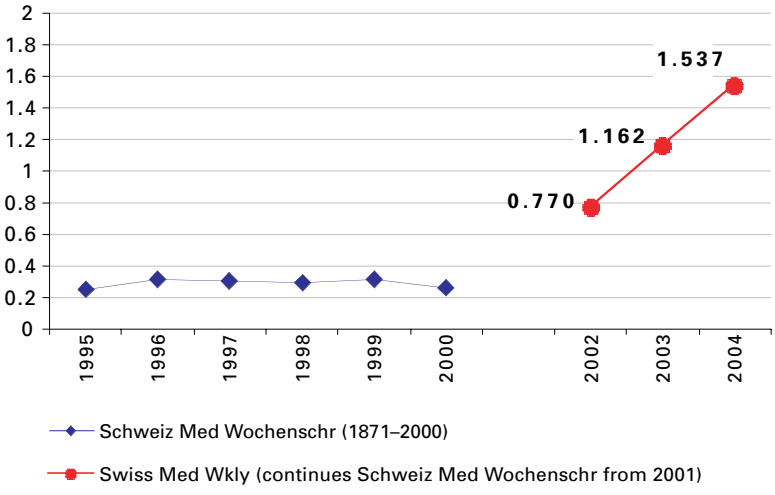

EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

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Letters to the editor: letters@smw.ch
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