REVIEW ARTICLE

Improving Adherence With Medication

A Selective Literature Review Based on the Example of Hypertension Treatment

Jan Matthes, Christian Albus

SUMMARY

Background: A common problem among patients with chronic diseases is poor adherence with prescribed medication. Studies have shown that certain interventions can improve adherence and clinical outcomes.

Methods: We selectively searched the PubMed database for publications on the treatment of hypertension that contained the terms "adherence," "drug," "treatment, "outcome," "hypertension," and "randomized controlled trial."

Results: The interventions studied were highly varied, ranging from the use of calendar blister packs to complex patient education programs. 62% of the studies that we identified documented an improvement in adherence after an intervention (median Cohen's d = 0.52). In 92% of cases, improved adherence was associated with a significant improvement in clinical end points (median Cohen's d = 0.34).

Conclusion: The promotion of adherence to prescribed medication is clearly desirable. Studies on the treatment of hypertension have shown that attempts to improve adherence often fail. In most studies, however, improved adherence led to better clinical outcomes. Simplification of drug regimens (e.g., reducing the number of pills taken per day) is the single most effective way to promote adherence. Moreover, the findings of studies on the treatment of hypertension and other diseases suggest that shared decision-making should be the basis of physician-patient discussions about medication. Suitable medications can also be chosen in order to maximize safety and efficacy even if adherence is incomplete. It would also be desirable for studies on the promotion of adherence to be carried out in Germany, under the specific conditions that prevail in our national health-care system.

▶ **Cite this as:**
Matthes J, Albus C: Improving adherence with medication—a selective literature review based on the example of hypertension treatment. Dtsch Arztebl Int 2014; 111(4): 41–7. DOI: 10.3238/arztebl.2014.0041

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The term "compliance," which was used most often in the past, is often understood from a perspective of a paternalistic or maternalistic role of the treating health professional, in the sense of not following the drug regimen prescribed by the doctor. The term "adherence," which is the preferred term today, is based on the therapeutic alliance between patient and treating physician and thus explicitly refers to responsibilities on both sides. The concept of shared decision making can be considered as accepted in this setting *(Box 1)* (1, e1–e3). It is also consistent with the definition of adherence as proposed by the World Health Organization (WHO): "The extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (2). Adherence in the wider sense describes the extent to which a patient follows a treatment plan. In industrialized countries, medication adherence for chronic diseases is often only around 50% (2). The forms and patterns of adherence (or non-adherence) with medication and the parameters for measuring these are varied. The measure used most often is determining the proportion of drug doses that are prescribed and then actually taken. According to Dunbar, adherence and its measurement can be placed in one of three categories (3). The first category is that of the quantity of medication, and further differentiation comes under that category—for example, between the proportion of medical drugs taken relative to the doses laid out in the treatment plan (the prescribed doses), the proportion of medications taken in the correct dosage, or the taking of the medication doses at the time stipulated in the treatment plan (4–6). The term "persistence" describes the proportion of patients who (still) follow the prescribed drug treatment at all, or "the duration of time from initiation to discontinuation of therapy" (4, 5). Depending on the observation period, it is difficult to distinguish between non-persistence and temporary drug holidays. Relative to the overall prevalence of non-persistence, primary non-persistence—that is, a situation in which a prescribed medication regimen is not even started—represents a lower proportion of patients, at 5%, but still a relevant proportion (4, e4–e6). Dunbar's second category attempts a qualitative evaluation of adherence as "good" or "poor" (non-adherence) (3). However, the

definition of what is considered "good" adherence varies notably in different studies—for example, with threshold values of ≥ 80% to ≥ 95% regarding the ingestion of prescribed doses (6). The third category comprises combined adherence indices that associate different behaviors (for example, taking medication, turning up for doctor's appointments, abstaining from nicotine) and/or awareness/knowledge (for example, about the treatment or disorder).

Studies have shown that low adherence is associated with a reduction or total absence of therapeutic success, reduced quality of life, and higher treatment costs, among others; good adherence, by contrast, is associated with lower mortality in clinical studies (2, 7, 8). Many studies have been conducted of the question of which factors can influence adherence with medication and of which measures can increase compliance with regard to medication therapy (2, 6, 9, e7–e10). In this article, we provide an overview of studies that investigated whether measures to promote adherence influenced compliance on the one hand and clinical end points on the other hand. Our focus was on studies of arterial hypertension, since hypertension is a clinically relevant example of a common disorder with serious consequences, which can be treated effectively, but whose therapy in all experience has been associated with unsatisfactory adherence (2, 10, e11, e12).

Methods

We conducted a PubMed search using the search terms "adherence," "drug," "treatment," "outcome," "hypertension," and "randomized controlled trial," without any restrictions on date of publication. We identified in the search results the prospective, randomized, controlled studies of antihypertensive therapy, in which effects were reported for end points regarding adherence to medication as well as lowering of blood pressure. Further inclusion criteria were: a rate of participants dropping out of the study of <20% and an observation period of at least six months. Our research results were compared with and augmented by a meta-analysis by Kripalani et al. and a review article by Haynes et al. (11, 12). See *eBox* for the effect size calculation.

Results

The PubMed search yielded 88 hits for the search terms used; the number was reduced further by 16 by restricting the selection to the article type "clinical trial." The remaining publications included 21 randomized clinical intervention studies of end points regarding hypertension and adherence. Two of these studies were excluded as the results regarding adherence were not shown (e13, e14). Five of the remaining 19 studies did not meet the inclusion criteria rate of study dropouts <20% or a minimum observation period of six months (e15–e19). Seven further studies that met the requirements were taken from the articles by Kripalani et al. and Haynes et al. (11, 12).

As expected, very different measures aiming to promote adherence were studied, ranging from the use of calendar blister packs to combination preparations to comprehensive educational events, regular personal encounters, or the use of telephone based computer systems *(Table 1)*. Many studies combined several measures (complex interventions). The adherence end points were similarly heterogeneous and ranged from patients' self assessments on the basis of validated scores to the proportion of drug prescriptions actually filled to electronic registration of frequency and timing of medication intake. Clinical end points comprised systolic and/or diastolic blood pressure measurements, their decrease during the study period, or achieving the target blood pressure. Blood pressure measurements were partly taken on an outpatient basis, partly in hospitals or doctors' offices.

13 of the 21 studies (62%) showed a positive effect of the intervention under study on adherence compared with a control group *(Table 1a, b)* (13–25); eight studies did not *(Table 1c, eTable)* (26–33). In 12 of the 13 studies showing a positive effect on adherence, at least one end point regarding antihypertensive therapy improved *(Table 1a)*, in one study this was not the case (21). One study showed a significant improvement in clinical end points, but not of the collected adherence parameters *(Table 1c)* (31). The effect sizes estimated by using Cohen's d varied regarding the adherence end points from small to large (0.29–2.89), with a median of 0.52. Regarding the hypertension end points, the effect sizes were mostly small (0.16–0.80, median 0.34).

Discussion

Using the example of antihypertensive medication, we found that of 21 randomized controlled studies of the effect of adherence-promoting measures on clinical end points, only 13 affected therapeutic compliance positively. The finding is consistent with other reviews and meta-analyses of various diseases, where 30–50% of studies did not show that the measures under study improved adherence (10–12, 34). On the other hand, it should be noted that 12 out of 13 studies (92%) in which compliance was affected positively showed additional significant effects on antihypertensive treatment end points in the intervention groups. Kripalani et al. conducted a meta-analysis of intervention studies for different diseases (12). For those studies that improved adherence as well as clinical end points, these authors found rather remarkable effect sizes compared with control groups (here: Cohen's d): 0.27–0.89 (median 0.55) for adherence and 0.29–1.58 (median 0.66) for clinical end points. In the studies on hypertension treatment that were analyzed for the present work, the effects sizes for the clinical end points were markedly lower. In terms of limitations, one has to note that in the studies considered by Kripalani et al. and by us that found positive effects regarding adherence, often only a proportion of the end points that had been defined a priori were significantly affected.

In some studies included in our review it seems easy to explain why they did not yield positive results. One study was successful in terms of the hypertension end

TABLE 1a

Randomized controlled studies of therapy with antihypertensive drugs, in which the intervention under study had positive effects on adherence as well as on clinical end points

Study	Type of intervention/case numbers (control vs intervention)	Effects on adherence and clinical end points
(13)	• Weekly for 6 months: monitoring medication intake, finding out patients' knowledge about hypertension, advice given using a telephone based computer system • n = 230 vs n = 230	After 6 months: • Pill count* • Blood pressure systolic (n.s.) and diastolic*
(14)	• Instructing patients to take their own blood pressure measurements and adjusting medication intake to individual daily routines • Every 14 days: face to face meeting for support purposes • n = 19 vs n = 20	After 6 months: • Pill count (ES 0.57)* • Diastolic blood pressure (ES 0.58)*
(15)	• If required, initial adjustment of diabetes medication and antihypertensive medication as suggested by the pharmacist • Structured diabetes education, including the importance of adherence and lifestyles that negatively affect blood pressure; providing patients with information leaflets • 20 minute telephone consultations with the pharmacist every 8 weeks (topics: current medication, importance of adherence and treatment plan, possible concerns on the part of the patient) • n = 79 vs n = 77	After 6 months: • Proportion of adherent patients on the basis of self assessment by Morisky score* • Reduction in systolic (ES 0.54)* and diastolic blood pressure (ES 0.41)* • Proportion of patients with blood pressure <130/80 mm Hg*
(16)	• Individual patient education about medication (about 1h) • Consultation with a pharmacist every other month (topics: adherence, medication if needed, prescriptions) • Packaging the drugs in calendar blister packs • n = 76 vs n = 83	After 6 months: • Ratio of medication taken to medication prescribed (ES 2.06)* • Proportion of patients with adherence of at least 80%* • Blood pressure systolic (ES 0.49)* and diastolic (n.s.)
(17)	• Intervention 1: three telephone consultations with patients within 6 months (topics: reminder about appointments, finding out about medication intake; praise or encouragement if needed) • Intervention 2: three postal deliveries of written information materials within 6 months (topics: information about hypertension and correct medication intake; positive reinforcement; reminder of appointments) • n = 182 vs n = 184 and n = 172	After 6 months: • Ratio of medication taken to medication prescribed (ES 0.44 and 0.52)* • Blood pressure systolic (ES 0.23 and 0.24)* and diastolic (ES 0.46 and 0.27)*, measured by primary care physician, using Riva-Rocci • Difference of blood pressure systolic (ES 0.80)* and diastolic (0,21)* compared with baseline values for intervention 1
(18)	• Documentation of blood pressure measured electronically by patients themselves on three days per week (after receiving written instructions and instructions over the telephone) • n = 100 vs n = 100	After 6 months: • Ratio of medication taken to medication prescribed (electronically recorded by Monitoring Events Medication System") (ES 1.11)* • Proportion of patients with good adherence (ratio of medication taken to medication prescribed 80–100%)* • Proportion of days when the correct dose was taken (ES 0.29)* • Proportion of days when medication was taken at the correct time (ES 0.33)* • Blood pressure systolic (n.s.) and diastolic (n.s.), electronic double measurement • Reduction of blood pressure over the study period: systolic (n.s.), diastolic (ES 0.31)*
(19)	• Three quarterly meetings with pharmacists (topics including patient education, offer to check adherence) • Written information material • n = 99 vs n = 98	After 9 months: • Proportion of patients with poor adherence (based on modified Morisky score)* • Proportion of patients who reached target blood pressure* • Blood pressure systolic (ES 0.40)* and diastolic (ES 0.33)*, electronically measured by nurses
(20)	• 6-monthly individual meetings with pharmacists over 36 months (topics including identifying potential problems with adherence, importance of therapy for general health, administration of medication) • Individual plans for further proceedings, based on the results from the meetings • 6-monthly group meetings (up to 20 participants) with pharmacists over 36 months (topics including adherence, risks of self-medication, dosages) • n = 100 vs n = 100	After 36 months: • Adherence on the basis of Morisky score* • Proportion of adherent patients on the basis of ratio of prescriptions issued to prescriptions filled (adherence here: 80–115%)* • Proportion of patients who reached target blood pressure*
(22)	• Pill count • Including relatives in the program • Information brochure • n = 457 vs n = 417	Over 6 months: • Ratio of medication taken to medication prescribed (ES 1.91)* • Proportion of medication taken at the correct time (ES 2.89)* • Blood pressure systolic (ES 0.17)* and diastolic (ES 0.16)*, triple determination by electronic device
(23)	• Individual patient education to achieve independent blood pressure monitoring, promote adherence, and enable detection of adverse events • 10-minute telephone consultations with study nurse after 1 week, 1, 2, and 4 months (topics: questions about dosage, potential problems with medication, invitation to get in touch via telephone if required) • n = 76 vs n = 74	After 6 months: • Proportion of days when the correct dose was taken relative to the respective prescription (electronic registration using Electronic Drug Event Monitor) (ES 0.41)* • Decrease in systolic (ES 0.46)* and diastolic blood pressure (ES 0.34)*, measured by using permanently installed sphygmomanometer in hospital

(24)	• Calendar blister pack • n = 38 vs n = 47	Over 12 months: • Calculated number of days covered by prescribed medication (medication possession ratio) (0.47)* • Number of prescriptions collected in time (ES 0.58)* • Blood pressure systolic (n.s.) and diastolic (ES 0.47)* • Hypertension-associated morbidity, n.s. • Admissions to hospital and visits to outpatient department, n.s.
(25)	• Written information material about disease and treatment • Lifestyle diary • Monthly blood pressure measurement by pharmacist • Monthly meeting with pharmacist for 30–50 minutes (topics: current medication, lifestyle, factors affecting blood pressure, problems with the therapy if required) • If required, recommendations for change in therapy to treating physician • n = 117 vs n = 118	After 6 months: • Proportion of patients with good adherence (= at least 80% of doses prescribed were taken)* • Blood pressure systolic (ES 0.20)* and diastolic (ES 0.24)*, measured by using sphygmomanometer in hospital • Reduction in systolic (ES 0.25)* and diastolic blood pressure (ES 0.23)*

* Statistically significant effects in favor of the intervention group (as a rule p<0.05);
n.s.: non-significant, ES: effect size, estimated as Cohen's d.

TABLE 1b

Randomized controlled study of antihypertension therapy, in which the intervention under study had a positive effect on adherence but not on clinical end points

Study	Type of intervention / case numbers (control vs intervention)	Effects on adherence and clinical end points
(21)	• Brochure and two-monthly telephone consultations (focus: positive reinforcement, self-efficacy) • n = 131 vs n = 125	After 12 months: • Proportion of days with correct medication intake (by electronic registration of pack opening)* • Blood pressure systolic (n.s.) and diastolic (n.s.), measurement taken in the context of usual primary care physician visits by practice nurse or practice assistant, using sphygmomanometer

* Statistically significant effects in favor of the intervention group (as a rule p<0.05);
n.s.: non-significant

TABELLE 1c

Randomized controlled study of antihypertension therapy, in which the intervention under study had no positive effect on adherence but on clinical end points

Study	Type of intervention / case numbers (control vs intervention)	Effects on adherence and clinical end points
(31)	• Information brochure • Ambulatory blood pressure measuring device • "Diary" (log book) • Access to telephone-based, IT-supported, management program (feedback to patients and treating physicians) • n = 112 vs n = 111	• Scores based on the time period covered by medication as per calculated time period covered by the prescribed medication# • Mean ambulatory blood pressure over 24h* • Mean ambulatory blood pressure during daytime* and at nighttime* • Blood pressure as measured electronically at the primary care physician's office*

*Statistically significant effects in favor of the intervention group (as a rule p<0.05); n.s.: non-significant statistically when comparing the groups with one another; # p = 0.07

points, but the effect on adherence did not reach significance (p = 0.07) (31). The calculated statistical power regarding the adherence end point was not reached, because the number of included patients was notably below the intended number (111 and 112, instead of two groups of 250 each). In another study, adherence at baseline was as high as 98%, blood pressure regulation was initially also already good, at <140/80 mm Hg (29). Even if an improvement in adherence could have been noted in this setting it is highly questionable whether this would have sufficed for a clinically relevant effect on blood pressure.

A comparison of the studies we identified did not clearly show what makes an intervention effective, or more effective than others. One reason, among others, is that most studies combined several individual measures. Kripalani et al. in their meta-analysis concluded that individual measures that target medication intake behavior directly, are most likely to be successful regarding adherence and are most effective, primarily those that aim to simplify therapeutic schemes (for example, a reduction in the daily number of medication intakes, or packaging medications in calendar blister packs; Cohen's d as effect size [ES]: 0.89–1.20)

BOX 1

Shared decision making in the therapeutic setting (1)

- The interaction between doctor and patient aims to identify the appropriate therapy by reaching a decision jointly by means of communication
- This entails explaining the current scientific evidence on the background of a doctor–patient partnership orientation.
- The best possible decision about therapy should be reached according to clinical demands and by recognizing the patient's preferences.

(12). In the hypertension studies we identified, using calendar blister packs in one case improved both adherence and blood-pressure control; in another study, the outcome was unsuccessful for compliance as well as antihypertension treatment. A study investigating the use of fixed combinations of antihypertensive drugs was unsuccessful, which seems to be due to the baseline conditions (29). The data are not sufficient to assess the use of the much discussed polypill, which contains substances to treat different disorders and diseases, even though indications are that adherence is improved compared with the use of monopreparations (e20, e21). The reasons for a lack of adherence are multifarious and comprise the diversest of factors *(Box 2)* (2, 9, 10, 35, 36). The list of factors with a negative impact can be contrasted with a list of adherence-promoting factors that mirrors it in many instances *(Box 2)* (9, 35, 36). Accordingly, Kripalani et al. found improved adherence for other measures too. These included, for example, improved information for patients (for example, individual training sessions or group training, printed information materials; ES 0.35–1.13), testing patients' knowledge and awareness (for example, during personal conversation or via computer communication; ES 0.27–0.81), or a close observation period (including the use of reminders; ES 0.43–0.86) and adherence monitoring (ES 0.27–1.20) (12). The latter two items are among the successful educational interventions that many studies have consistently indicated (10–12). Of note is the fact that the effect sizes of the more complex interventions range between weak and strong (ES 0.43–1.2) and that the combination of different approaches does not necessarily bring about any further improvement of the effect on adherence (12). Many of the studied interventions are part of strategies that can be used to pursue the concept of shared decision making (1, e22). Indeed, promoting shared decision making can, in suitable patients, improve therapeutic success, as has been shown by a study of hypertension treatment (37). However, data on this issue from clinical studies are insufficient so far.

It seems obvious to conclude that the selection of the drug can contribute to improving adherence if one considers that the reasons for non-adherence include adverse drug effects (possibly specific to the effective substance). The side effect profiles are thus being

BOX 2

Factors that influence adherence

- **Factors that improve adherence (2, 10, 35, 36):**
  - Long term medication intake (>5 years) (35)
  - Awareness of the necessity of long term treatment
  - Low number of daily drug intakes
  - Older age (for example, >60 years for anticonvulsive or antihypertensive drugs) (2, e23)
  - Marital status: married
  - Social support
  - Satisfied with the therapy
  - Experience of effectiveness
  - Systematic, close follow-up
  - Good awareness and knowledge of therapy
  - Short waiting times when visiting the doctor and between visits
- **Factors that impair adherence (2, 35, 36):**
  - Chronic disorder
  - Few or no symptoms
  - Long duration of treatment
  - Several doses required every day (from only >2/d) (9)
  - Complex treatment schemes
  - Adverse effects or fear of such effects
  - Measures that impair everyday life
  - Younger age (for example, <60 years for antihypertensive medication) (e23, e24)
  - Male, single
  - Low level of education
  - Lack of support
  - Lack of communication between doctor and patient
  - No or insufficient information
  - Ignoring the problems with adherence

discussed in association with data on current hypertensive drugs of choice, according to which adherence seems best for therapy with angiotensin 1 receptor blockers (38). Furthermore it seems plausible that pharmacotherapy should be planned while fully expecting unsatisfactory compliance. A concept that may be useful in this setting is that of "forgiving" drugs. The extent to which a medical drug "forgives" if it is taken irregularly depends, among others, on the rate at which its effect wears off ("off-rate") and the time taken until its effect sets in (again). An analysis of simulated treatments over a time period of 256 days showed that for many hypertensive drugs, a mean intake of 75% of prescribed doses means that a significantly impaired mean blood pressure reduction is to be expected (39). According to the study, however, no loss of systolic blood pressure reduction would be expected for amlodipine (off-rate <1 mm Hg/d), whereas for enalapril (off-rate 12 mm Hg/d) the reduction is only about 10 mm Hg with an otherwise equally effective dose. It should be noted, however, that to our knowledge, no clinical end point studies of the concept of forgiving antihypertensive drugs exist so far.

Summary and conclusion

Attempts to improve medical adherence have often failed, which is confirmed by the available studies of hypertension treatment. If improvement of adherence is successful, however, positive effects for clinical end points can also be expected for many of the patients. Studies of different diseases have shown that measures to simplify medication therapy schemes, such as reducing the number of tablets and the frequency of intake, are the most effective single measures to improve adherence, and they are rather easy to implement. Further effective measures include, for example, patient information about their disease and treatment (positive and negative aspects), active integration of patients, and consideration of factors affecting adherence in general *(Box 2)* as well as of individual possibilities and needs. This supports the recommendation of making shared decision making *(Box 1)* the basic principle of the prescribing consultation (2, 40). In case individual measures are not sufficiently effective, complex interventions may be considered, such as are available in the context of "patient education on hypertension" and rehabilitation measures, for example. The individual selection of suitable medications should consider the adherence that is to be expected and, if needed, it can be shaped in such a way that the medication therapy is as effective and safe as possible, even in case of unsatisfactory compliance.

KEY MESSAGES

- Adherence with medication is unsatisfactory for chronic disorders such as arterial hypertension.
- Randomized controlled studies of promoting adherence in antihypertensive therapy have shown an improvement in adherence in 60% of patients, which in the majority of studies was associated with improvement in at least one clinical end point.
- The most effective single measures to promote adherence are based on simplifying therapeutic schemes.
- Many adherence-promoting measures entail the active integration of the patient in the therapy, so that for example shared decision making as the basis of the consultation seems worth recommending.
- By selecting suitable medication, adherence promotion can be supported while at the same time counteracting unsatisfactory adherence.

Conflict of interest statement
Professor Albus has received honoraria for consulting from UCB Pharma. He has received honoraria from Berlin Chemie and Actelion Pharmaceuticals for preparing continuing medical education events.

Dr Matthes declares that no conflict of interest exists.

Manuscript received on 31 May 2013, revised version accepted on 30 July 2013.

Translated from the original German by Dr Birte Twisselmann.

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A Selective Literature Review Based on the Example of Hypertension Treatment

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eTABLE

Randomized controlled studies of therapy with antihypertensive drugs, in which neither adherence nor clinical end points were affected in favor of the intervention under study

Study	Type of intervention / case numbers (control vs intervention)	Effects on adherence and clinical end points
(26)	• Calendar blister pack • n = 85 vs n = 86	After 3 months: • Self assessment of adherence (n.s.) • Pill count (n.s.) • Systolic blood pressure (n.s.), mean value from the 2nd and 3rd measurements of a total of 3
(27)	• Verbal and written information on the active ingredient (hydrochlorothiazide) from the pharmacist • Monitoring the learning effect resulting from the usual patient education • Identifying and solving problems with the medication • Checking the success of the intervention • n = 30 vs n = 34	After 6 months: • Proportion of patients with hydrochlorothiazide confirmed in plasma (n.s.) • Self assessment of adherence (n.s.) • Ambulatory blood pressure measured electronically: systolic (n.s.) and diastolic (n.s.)
(28)	• Intervention group 1: ambulatory blood pressure measurement by patients • Intervention group 2: ambulatory blood pressure measurement by study personnel every four weeks • Intervention group 3: combination of the two measures described above • n = 34 vs n = 34 and n = 33 and n = 35	After 6 months: • Self assessment (n.s.) • Pill count (n.s.) • Reduction in diastolic blood pressure (n.s.)
(29)	• Combined preparation instead of two monosubstances • n = 104 vs n = 103	After 1, 3, and 6 months: • Pill count (n.s.) • Blood pressure systolic (n.s.) and diastolic (n.s.), double measurement performed by study personnel, using sphygmomanometer
(30)	• 30-minute motivation training after 3, 6, 9, and 12 months (topics: identifying and resolving the discrepancy between behavior and objectives) • n = 79 vs n = 81 (adherence) and n = 95 vs n = 95 (blood pressure)	After 12 months: • Proportion of days with correct intake of medication (by electronic registration of pack opening) (n.s.) • Blood pressure systolic (n.s.) and diastolic (n.s.), measurement in the context of normal primary care physician visits by practice nurse or practice assistant, using sphygmomanometer
(32)	• Intervention group 1: Care delivered during working hours by an occupational health physician rather than outside working hours by a primary care physician • Intervention group 2: Patient education on aspects of hypertension (including sequelae, therapy, importance of adherence) • Intervention group 3: Combination of the two measures described above • n = 87 (care delivered by occupational health physician), n = 57 (care delivered by primary care physician), n = 80 (patient education), n = 64 (no patient education)	After 6 months: • Proportion of patients with good adherence (= intake of a minimum of 80% of medication doses prescribed) (n.s.) • Proportion of patients with diastolic blood pressure <90 mm Hg (n.s.)
(33)	• Discussion with a study nurse of patients' questions/concerns about the medication at the start of the study (20 minutes) and after 2 months (10 minutes) • n = 117 vs n = 128	After 6 months: • By electronic recording of: • Proportion of days when drugs were taken punctually (every 24 ± 6 h or 12 ± 3 h) (n.s.) • Proportion of days when the correct numbers of pills were taken (n.s.) • Ratio of drugs taken to drugs prescribed (n.s.) • Blood pressure systolic (n.s.) and diastolic (n.s.)

n.s.: statistically not significant when comparing groups with one another

eBOX

Effect size

The effect sizes were estimated according to Cohen's d by using the following formula:

$$d = \frac{\bar{x}1 - \bar{x}2}{\sqrt{\frac{s_{x1}^2 + s_{x2}^2}{2}}}$$