Strategies to Improve Drug Adherence

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Introduction

The demographic development of increasing numbers of elderly patients with chronic diseases requiring continuous polypharmacy represents a challenge for medical care. At present, 30–40% of all German patients >65 years are prescribed four or more different medications, and this number is expected to increase.[1,2] Non-adherence to medical treatments is an increasingly recognized cause of adverse treatment outcomes and increased health care costs,[3–5] for example, that caused by preventable admissions for heart failure[5–9] or coronary artery disease.[10–14] Average estimated rates of adherence may be as low as 50–80%.[10,15] A typical study reports that of the prescribed medications after discharge of from hospital, only about one-third were regularly taken, whereas two-thirds went to waste.[16] In Germany, the annual costs due to poor compliance in medical therapy are estimated up to 10 billion Euro.[17]

Definitions

Drug compliance is defined as the extent to which patients follow medical instructions.[17] Today, the term 'compliance' is used less frequently because it implies that only the patients is responsible for the medical treatment. The term 'adherence' has now replaced 'compliance', because it reflects a less paternalistic physician–patient relationship, and includes the responsibility of the caregivers. Adherence has been defined as 'the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result'.[4] Some patients may never start treatment and this type of non-adherence has been named non-acceptance. Medication adherence also includes the concept of persistence taking into account the willingness to take a prescribed medication throughout the overall duration of drug therapy.[4] The degree of accordance of therapeutic goals of patient and therapist is defined as 'concordance'. The definition of 'concordance' has changed over time from one which focused on the consultation process, in which doctor and patient agree on therapeutic decisions that incorporate their respective views, to a wider concept which stretches from prescribing communication to patient support in medicine taking.[18] For practical reasons, many studies on this topic report the percentage of doses taken during a time period, however, this does not distinguish between individuals that have executed the regimen well but quit compared with individuals that took only part of the doses but continued over the whole observation period.

Patient Characteristics Influencing Adherence

Adherence has been found to be better when the patient accepts the severity of his illness, trusts the therapist, and believes in the effectiveness of the recommended therapeutic measures.[4,19–22] Non-adherence is, among other factors, negatively associated with the level of education and the stability of family backgrounds. In addition, important factors influencing adherence include the affordability of the therapy.[4,19,20,23–26] Neurological and psychiatric disorders including dementia, memory problems, depression, and anxiety as well as impaired visual and motor skills are associated with reduced adherence.[27–31] Furthermore, the susceptibility to adverse effects of drugs in individual patients such as cough with angiotensin-converting enzyme inhibitors or statin myopathy reduces the tolerability of drugs. The underlying genetic and acquired causes of many adverse drug effects are only partially understood and require further research.[5]

Adherence in Cardiovascular Disease

Adherence to prescribed medication predicts outcome. In a population-based sample of >137 000 patients under the age 65 with diabetes, hypertension, hypercholesterolaemia, and congestive heart failure, hospitalization rates as well as health care costs were significantly lower for patients with high medication adherence.[32] In the *Heart and Soul* study examining the impact of self-reported adherence, cardiovascular events were almost twice as high in non-adherent study participants and remained independently predictive of adverse cardiovascular events after adjusting for baseline disease severity and known risk factors.[10] In >54 000 new statin users in the Netherlands, adherence to statin treatment for at least 2 years was associated with a 30% reduction in acute myocardial infarction with even better results in patients taking higher doses.[12] Similar results were obtained in a study examining the effects of medication adherence on long-term mortality in a cohort of >31 000 Canadian AMI survivors.[13] In a retrospective cohort study of >229 000 patients in Israel, the extent of reduction of all-cause mortality was directly associated with adherence to statin intake (relative Hazard Ratio 0.53 for patients with ≥90% of treatment days covered by statins compared with <10%).[11] Another example of the importance of adherence outcome is an analysis of the CHARM study that assessed the effects of treatment with the angiotensin receptor blocker candesartan in 7600 patients with chronic heart failure.[5] Good adherence was defined as an intake of >80% of the prescribed dose and correlated with a lower

risk of death. The extent of risk reduction associated with good adherence was markedly greater than the risk reduction conferred by the study drug candesartan itself. Adherence to placebo resulted in a similar reduction of mortality compared with good adherence to candesartan (hazard ratio 0.66 in the verum group and 0.53 in the placebo group).[5]

The 'Healthy Adherer' Phenomenon

Good adherence to both placebo as well as to drug treatments is associated with reduced mortality.[33] This observation supports the concept of the 'healthy adherer' effect, whereby adherence to drug treatment represents a surrogate marker for overall healthy behaviour. The hypothesis is that people who adhere to healthy lifestyles also tend to take better care of themselves by greater adherence to prescribed treatments. Indeed, in a recent study on the correlation between statin adherence and the risk of non-medication related accidents and diseases, it was shown that good statin adherence was associated with a lower probability of having motor vehicle accidents or workplace accidents as well as suffering from diseases unrelated to statin use. The lower probability of having accidents was related to a more health-conscious lifestyle, such as using screening services.[34] These observations show that poor adherence identifies individuals at increased risk. The challenge is to find a comprehensive approach to enhance the factors underlying the 'healthy adherer' phenomenon.

Importance of Adherence for Drug Safety

The problems of poor medication adherence are not limited to drug discontinuation but include inappropriate use of drugs.[35,36] Adverse events of medication have been observed in ~5% of all treated patients. They are the cause of 3–5% of all hospital admissions.[37–39] In the majority of cases adverse drug reactions are associated with incorrect drug use.[37,40] As much as two-thirds of adverse drug events following hospital discharge have been estimated to be preventable with an improved management of adherence and better monitoring: at least one-third of adverse events is caused by an error in drug administration, and in another third the severity of the adverse event could have been significantly reduced if health care delivery had been optimal.[41]

Measures to Quantify Medication Adherence

Adherence can be assessed through direct or indirect methods. Direct methods such as the measurements of blood levels are able to yield quantitative data, but they are not always applicable under the conditions of routine practice, and for many drugs blood tests are not available. Indirect methods include patient questionnaires, pill counts, statistics on repeated prescriptions, electronic monitoring systems, and patient diaries. None of these methods will provide 100% robust data. For example, pill counts can be manipulated by the patient by pill dumping. The combined evaluation of electronic openings, pill counts, and interviews may be needed to reveal openings without pill intake.[42] A method used in larger populations is the estimation of the days covered by medication through the calculation of the time span covered by repeated medical prescriptions and the number of dispensed pills.[4] Newer developments, such as blister packs that electronically record the opening of compartments, may facilitate the assessment of adherence in the future and may allow a direct feedback for the patient.

Measures to Improve Medication Adherence

Counselling

A thorough dialog of the advantages and disadvantages of each prescribed drug during the patient's consultation is considered the basis for the improvement of drug concordance and adherence.[43,44] Motivational interviewing may be useful to frame an open discussion of the treatment rationale, the patient's fears, valued outcomes, or social pressures.[44,45] The value of the patient's choice should be reinforced. Rules for drug intake should be in written formats. The concept of reminders also involves the pharmacist, the nurse, and the patient's family. The patient and caregiver should not only receive information on the effects of the drug, its dose and the timing of intake, but also be given an explanation of the meaning and probability of potential adverse effects and interactions. Adherence to the medication should be actively discussed every time the patient returns to the therapist as practically as possible, e.g. by asking the patient to bring in the medication boxes for joint inspection and discussion. Several studies have suggested that forgetfulness is an important factor contributing to poor adherence.[46] This is one explanation for the observation that many effects of counselling are transient.[47] The challenge is to implement continuous counselling strategies.

Telephone counselling as a measure to improve drug adherence has been shown useful in a 2 year randomized controlled trial in >400 non-compliant patients receiving five or more drugs prescribed for the treatment of chronic disease (*Figure 1*). Regular telephone counselling by hospital staff (not the physician) for the improvement of drug adherence was found to be associated with a dramatic reduction in the risk of death.[48] The extent of the observed benefit (41% reduction of mortality with large confidence intervals) needs to be re-evaluated in independent

studies, however, the data strongly suggest that a simple intervention combining weekly communication with improved medication adherence may be more powerful in saving lives than many significantly more expensive health care measures.

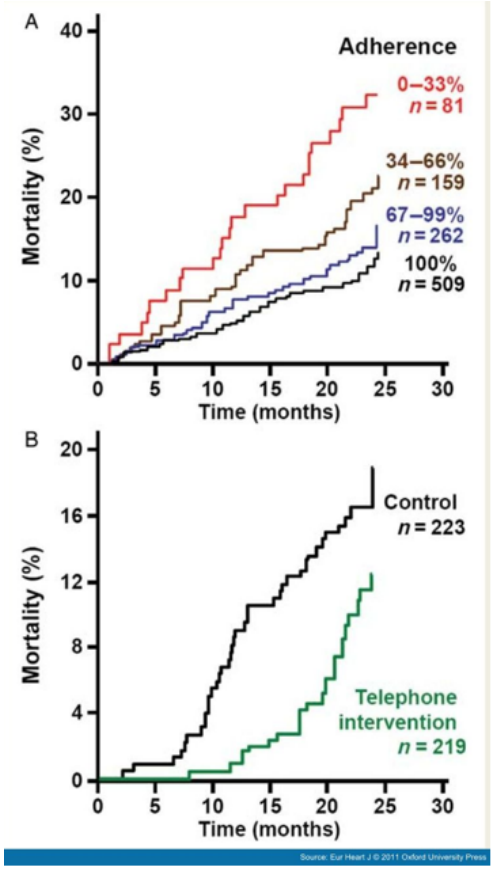

Figure 1.
(A) Kaplan–Meier estimates for 1011 patients receiving polypharmacy according to compliance score at the screening visit. Relative risks for death in patients with compliance scores of 0–33% and 34–66% were 2.9 and 1.8, respectively, compared with those who had a score of 67% or more. (B) Effect of telephone intervention by a pharmacist on all-cause mortality in patients receiving polypharmacy. Relative risk for intervention 0.59, P = 0.039 after adjusting for confounding factors; modified from Wu et al.[48]

Number of Daily Single Doses

The number of single doses to be taken daily is an important contributor to drug adherence and compliance.[15,49] A review of 76 clinical trials analysed drug adherence from data gathered by electronic monitoring (*Figure 2*). Increasing numbers of single doses were directly associated with dramatically decreasing adherence. Mean dose-timing compliance was likewise decreased with a higher frequency of single doses.[15] Simpler and less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes. The reduction of the number of tablets—independent of their content—is therefore an important measure for the improvement of drug adherence. Medication that is not effective (e.g. vitamins for the prevention of cardiovascular diseases) may cause harm by reducing the adherence for effective medications.

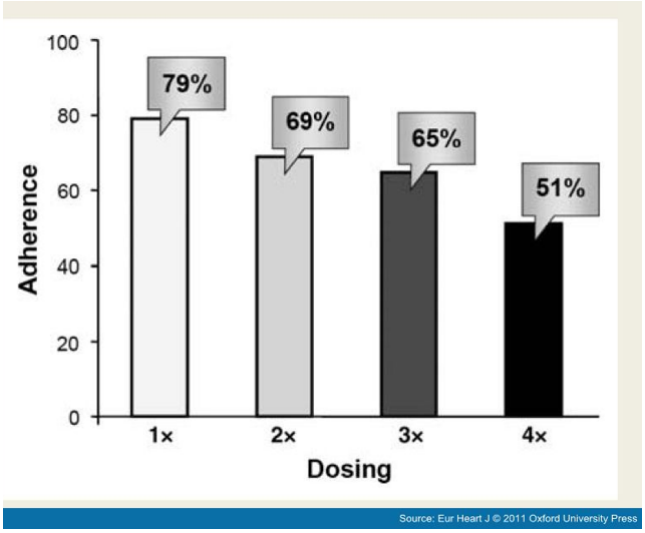

Figure 2.
Direct association between dosing frequency and medication adherence in studies using electronic monitoring across a variety of therapeutic classes; modified from Claxton et al.[15]

Fixed Combinations (Polypills) to Reduce the Number of Tablets

Fixed combinations, e.g. in the treatment of hypertension, can contribute to the reduction of the number of single doses, and therefore also improve drug adherence.[50] A calculation using a Markov model predicts that a preventive strategy using a fixed combination of acetylsalicylic acid (ASA), two antihypertensive drugs and statins may result in a 2 year gain in life expectancy which is cost-effective for developing countries.[51] The idea behind the 'polypill' is to take such findings one step further and offer the different drug substances in a single formulation instead of separate tablets or capsules for each individual drug. In an analysis of >11 900 patients on a fixed-dose combination, the relative risk of non-adherence was reduced by 26% compared with patients on free-drug component regimens.[50] Fixed-dose combinations could therefore be considered in patients with chronic conditions for the improvement of medication adherence, and subsequently the improvement of clinical outcomes. It has been suggested to combine several different drugs as a 'polypill', a concept that is currently being tested in clinical trials. At present, there is no clear consensus which kinds and doses of substances should be combined for optimal prevention.[51,52] A combination pill containing low doses of hydrochlorothiazide, atenolol, ramipril, simvastatin, and aspirin was compared with individual drugs given separately a randomized trial in primary prevention in India. This 'polypill' was well-tolerated and non-inferior to its individual components in lowering blood pressure and heart rate. It substantially lowered low-density lipoprotein (LDL) cholesterol and urinary 11-dehydrothromboxane B2, but to a degree that was

slightly less effective than simvastatin or ASA alone, which remains in part unexplained.[53] Drug registration of fixed combinations represents a challenge because justification of the contribution of each single constituent to the overall efficacy and the demonstration of a clinical advantage over the administration of the single constituents is required next to the respective safety information. In the case of adverse events it is difficult to identify the responsible component(s). Another important limitation is the reduced flexibility in the choice of both drug substances and the individual doses. For the individual patient the risk is high to receive either too much or too little of the polypill ingredients. Clearly, adherence can be improved using a polypill in comparison with the drugs taken separately, however, combination therapy does not necessarily require that different drugs have to be combined in one pill.[51]

Dose-dispensed Medicine

Dose-dispensing of medicine such as the use of time-specific packs containing each patient's medications is a relatively simple and efficacious method for the improvement of drug adherence. It maintains the advantages of an individual choice of drug and dose (*Figure 3*). This was tested in a clinical trial of a pharmacy care programme on medication adherence and persistence in hypertensive and hyperlipidaemic patients. A total of 200 elderly patients taking a mean of 9 ± 3 chronic medications were enrolled. Mean baseline medication adherence was 61%. The run-in phase was followed by a 6 month prospective observational study during which all patients received their medication in the form of pre-packed medication dispensers (blister cards). Part of the intervention was the education on indications, strengths, adverse effects, and usage instructions during each visit. The blister packs were labelled using a customized computer programme to meet the standards of the prescription. They were taken back to the control visits for pill counts. After 6 months of observational study phase medication adherence had increased to 97%, representing an absolute change in the adherence of one-third. The improved adherence was associated with improvements of systolic blood pressure and LDL-cholesterol. Following this observational phase the patients entered a 6 month randomized trial where patients were randomized to either pharmaceutical care with the time-specific blister pack, or to conventional medication administration. The aim of this second study phase was to determine the persistency of adherence. Among the patients assigned to usual care the medication adherence decreased to 69%, whereas it was sustained at 95% in patients under continued pharmacy care.[54] A controlled trial in >2400 patients >65 years revealed that a harmonized, structured pharmaceutical care programme improves the quality of life and the self-reported well-being, strongly suggesting that social and psychosocial aspects contribute to the effects of a pharmacy-based programme of weekly blisters.[55]

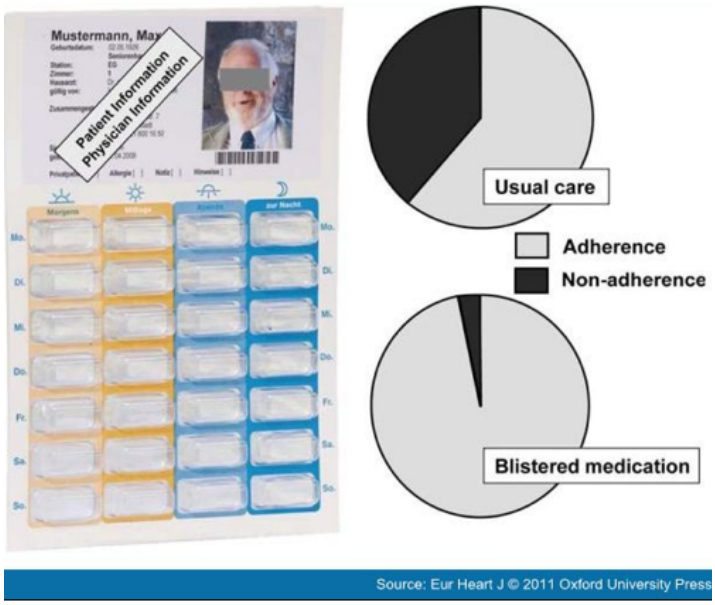

Figure 3.
Example of an individualized multidose adherence package containing a week's medication clearly labelled with day and time of administration, and the effect of providing medication in the weekly translucent blister punch cards combined with regular pharmacy-based counselling on adherence; modified from Lee et al.[54]

Unit doses may contribute to drug safety. The observation of adverse drug events has been shown to depend not so much on the intake of multiple medications as such, but rather on the dose and timing of administration. From a cohort study on the parameters responsible for the occurrence of adverse drug events it has been suggested 'that prevention strategies that focus on improving the systems by which drugs are ordered, dispensed and administered will prevent more events than patient risk stratification strategies'.[56]

Søndergaard *et al*.[57] followed the use of dose-dispensed medicine in 19 000 patients in Denmark. A detailed analysis was performed on a subgroup cohort of >4400 patients older than 65 years. Seventy-one per cent of the patients were women and 48% were in the age-group of 80–89 years. *Figure 4* depicts the hospitalizations during the 6 months before and 6 months after implementation of adherence aids. The analysis shows that the proportion of hospitalized patients decreased from 7 to 4%. At the same time, the average number of days in hospital decreased from 7 to 9 days before dose-dispending to 5–6 days thereafter. The total number of days in hospital in the cohort decreased by 62% from 15.4 days in the 6 month period before dose-dispending to 5.9 days in the 6 months after providing the medication in time-specific individual blister packs.

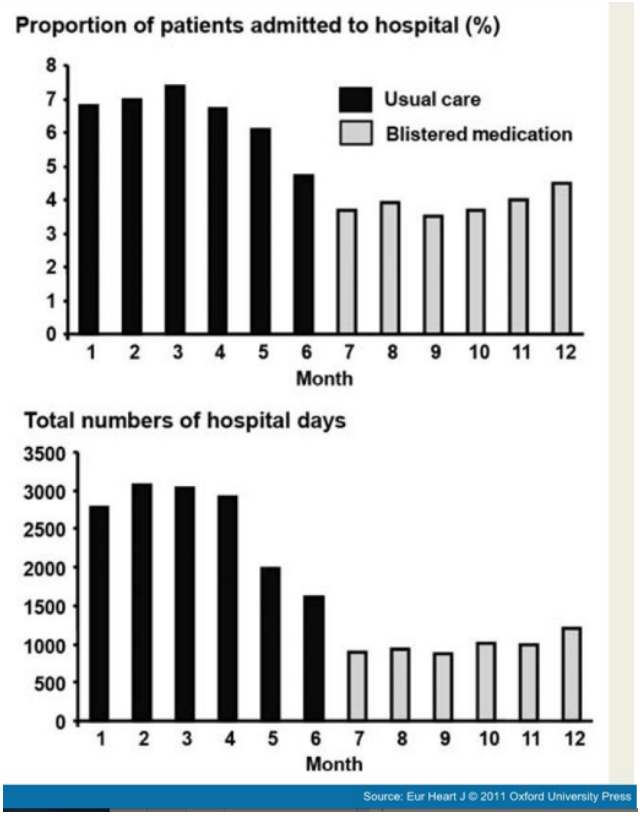

Figure 4.
Proportion of patients hospitalized and total number of days in hospital in a cohort of 4491 patients older than 65 years during the 6 months before and the 6 months after providing the medication in blister packs in Denmark; modified from Søndergaard et al.[57]

Conclusions

Increasing numbers of elderly patients require polypharmacy for chronic diseases. Non-adherence to medications is common and is associated with adverse treatment outcomes. Reduced adherence is an indicator of higher morbidity, adverse events, and costs. Practice guidelines on measures to improve adherence are urgently needed. Although research in drug adherence has only recently started obtaining broader attention, major reasons for insufficient drug adherence have been identified, and counter-measures proposed. Among these measures, an improved pharmaceutical care with thorough patient information and regular reminders by therapists, nurses, and pharmacists and the systematic use of pre-packed time-specific unit doses, e.g. in blister packs, have shown evidence of robust improvements of adherence. Optimising the adherence of medication administration may represent a powerful measure to reduce morbidity and mortality. However, because of the 'healthy adherer' effect, prospective clinical trials are urgently needed to test the effects of measures to improve adherence on clinical endpoints.

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