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An education-behavioural intervention improves adherence to statins

Research Article

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Abstract: Purpose: Effective treatment of hyperlipidemia is an important precondition for cardiovascular diseases. Unfortunately, adherence to lipid-lowering treatment is unsatisfactory. In order to improve adherence to statins, an intervention combining educational and behavioural components was tested in general practice settings. Methods: A total of 198 outpatients with untreated hyperlipidemia were enrolled in this open-label, prospective, randomised study. Patients were prescribed simvastatin, in initial dosage of 20 mg daily, and followed for 48 weeks. Intervention group received educational counseling at each visit (that is every 8 weeks); and were also asked to adopt a routine evening activity of their choice for a reminder. Control group obtained usual care. Primary outcome measure was patient adherence, expressed as medication possession ratio (MPR). Results: Patients' mean age was 59.6 +/- 9.1 years. Study arms differed in their level of adherence: mean ± SD MPR was 95.4±53.7% and 81.7±31.0%, for intervention and control group, respectively ($P<0.05$). Patients from intervention group found a reminder activity useful in over 90% of cases. Conclusions: Simple inexpensive educational-behavioural intervention proved to be effective in enhancing adherence to statins in hyperlipidemia. Given the health and economic consequences of non-adherence, these results may have high clinical, and practical usefulness.

Keywords: *Patient adherence • Statins • Hyperlipidemia • Education-behavioural intervention • Primary prevention • Secondary prevention*

1. Introduction

Hyperlipidemia is one of major risk factors for atherosclerosis and cardiovascular diseases. Its effective treatment is therefore of fundamental importance in the primary and secondary cardiac prevention. However, during the treatment of hyperlipidemia a large number of patients does not take their medicines as prescribed by healthcare professionals. This phenomenon, typical for therapy taking place in the outpatient setting, is known as non-adherence. It occurs with varying prevalence, depending on many factors, including disease, and prescribed medication type. According to the World Health Organization estimates, non-adherence occurs in about 50% of patients treated for chronic diseases [1]. Studies conducted in Poland confirm its high prevalence, even in case of patients suffering from such a symptomatic condition, as coronary heart disease [2,3]. However, non-adherence is particularly unsatisfactory in asymptomatic diseases, such as hyperlipidemia.

The most important consequence of patient non-adherence is ineffectiveness of prescribed treatments, and subsequently, failure to achieve full benefits from evidence-based therapies. In case of hyperlipidemia, a precondition for the patients to achieve full benefits of treatment is taking at least 80-90% of prescribed doses of statins. Taking a lower percentage of doses can lead to a reduced effectiveness of treatment, and increased risk of cardiovascular events, and mortality [4,5]. It was observed that patients who did not adhere to their statin therapy had nearly 40% higher risk of cardiovascular events during the 3-year follow-up, compared with the adherent ones [6]. Irregular statin treatment may even have similar outcomes as the complete lack of treatment [7,8]. Nevertheless, it was established that out of patients who have received lipid-lowering medication, after 6 months only 36% have satisfactorily adhered to the treatment, and 23% of patients failed to collect their repeated prescriptions at month 1. Over 40% of patients have discontinued their lipid-lowering treatment within first 6 months, and up to 50% within their first year [9-11]. On the other hand, the adherence to statins has been proven to significantly reduce

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cardiovascular morbidity, and mortality in both primary, and secondary prevention [10,12,13]. Unfortunately, a number of interventions tested so far had little impact on patients' adherence to the treatment for hyperlipidemia [14]. Therefore, it would seem advisable to test novel interventions for improving the patients' adherence under such circumstances. The purpose of this study was to assess whether the application of innovative educational and behavioural intervention has a significant impact on adherence to lipid-lowering treatment with statins in hyperlipidemia.

2. Methods

This study was an open-label prospective, randomized clinical trial that was conducted in primary care settings in Lodzdzkie voivodship, Poland. Patients with untreated hypercholesterolemia (total cholesterol >= 250mg/dL (6.465 mmol/L)), aged 40-80 years, were enrolled in the study. Exclusion criteria included mental illness, dependence on other people's assistance in medical care (e.g. use of a wheelchair, being bedbound) and/ or medication taking (e.g. manual disability, impaired visual acuity, etc.), being at risk of not completing the study due to alcoholism, psychoactive substance abuse, homelessness, etc., porphyria, unstable angina, NYHA class III or IV heart failure, acute infections, liver disease (cirrhosis), or significantly elevated transaminases (level >= 3 times above the normal values), allergy to simvastatin, or any other known contraindications to its use, pregnancy, and lactation. The sample size of 86 patients in each group was obtained by assuming medication possession ratio (primary outcome measure) of 95% for the intervention group and 85% for the control group with a common standard deviation of 20%, a power of 90% and α=0.05. Therefore, the study was designed to cover 200 patients in total.

All patients who were enrolled in the study have been prescribed simvastatin (Simvasterol, Polpharma SA, Poland), at the initial dose of 20 mg, to be taken once daily in the evening. The dosage was increased to 40 mg once daily, in the evening, if the total cholesterol level was still over 250 mg/dL (6.465 mmol/L) after 16 or 32 weeks of treatment.

Patients from the intervention group received counselling based on specially designed educational material at each visit (that is, every 8 weeks). The content of theis material was designed according to the results of the previous study [15] and included information about the risk of elevated cholesterol level, as well as the importance of adhering to the medication, and persistence with statin treatment. These patients were also asked to adopt a routine evening activity of their choice in order to remind them to take a medicine. During each control visit, investigator asked a patient if the reminder activity worked well for him/her, and if not, he helped the patient to chose another one. Patients in the control group received standard care. The observation period lasted 48 weeks.

The primary outcome measure was adherence to treatment, expressed by the medication possession ratio (MPR), which was calculated as the proportion of the number of days during which the patient was in possession of simvastatin, over the total number of days of the follow-up period. In addition, the percentage of patients who continued treatment and the length of continuous therapy were also assessed. For the statistical analysis, the descriptive statistics was used, where the qualitative variables were presented as mean ± SD, or median and quartile range, depending on the characteristics of distribution of variables. To assess the differences, parametric and non-parametric inference tests were used, depending on the distributions of variables. The chi2 test was applied in the analysis of qualitative variables. The level of significance was set as $P<0.05$.

3. Results

In total 198 patients aged 59.6±9.1 years (mean±SD) were enrolled in this study. The characteristics of the patients are provided in Table 1. Patients in both intervention and the control group had the same distribution of gender, age, weight, height, body mass index, and baseline lipid parameters.

Table 1. Characteristics of the studied population.

Parameter	Control group	Intervention group	P
Number (n)	89	107	-
Gender: F/M	68/21	80/27	NS
Age (years):	59.7 ± 9.5	59.5 ± 8.8	NS
Body weigth (kg):	73.8 ± 11.7	76.2 ± 13.5	NS
Height (m):	164.6 ± 8.4	164.5 ± 7.9	NS
BMI (kg/m^2):	27.0 ± 4.9	28.0 ± 4.1	NS
Total cholesterol:	279.3 ± 26.0 mg/dL (7.22 ± 0.67 mmol/l)	279.9 ± 23.4 mg/dL (7.24 ± 0.61 mmol/l)	NS
HDL cholesterol:	61.4 ± 16.9 mg/dL (1.59 ± 0.44 mmol/l)	59.3 ± 15.7 mg/dL (1.53 ± 0.41 mmol/l)	NS
LDL cholesterol:	179.3 ± 29.9 mg/dL (4.64 ± 0.77 mmol/l)	174.3 ± 29.7 mg/dL (4.51 ± 0.77 mmol/l)	NS
Triglycerides:	162.0 ± 71.5 mg/dL (1.83 ± 0.81 mmol/l)	176.9 ± 71.7 mg/dL (2.00 ± 0.81 mmol/l)	NS

BMI – body mass index, F – females, M – males, NS – P<0,05

Patients from the intervention group chose different activity to remind them to take their medication regularly; most often it was having an evening meal (53.3%, Table 2). At subsequent visits between 92-97% of patients declared their chosen reminder activities to be useful. At the first control visit, 8 weeks after the follow-up, only 6% of patients continuing the study changed the activity adopted by himself/herself for another one. During subsequent visits, this rate was even lower.

Table 2. Activities adopted by patients from the intervention group to remind them to take statin in the evening.

Activity	Number of patients	%
Having dinner	57	53.3
Brushing teeth	15	14.0
Together with other medicines taken in the evening	9	8.4
Watching TV in the evening	7	6.5
Before going to sleep	6	5.6
With the help of a box for distributing doses of medicines	2	1.9
After work	2	1.9
Switching off the night lamp	2	1.9
Drinking mineral water in the evening	2	1.9
Evening tea	1	0.9
Taking out false teeth	1	0.9
Evening toilet	1	0.9
Reading a book	1	0.9
About 8 (PM) o'clock	1	0.9
Total	107	100

The rate of patients continuing the therapy decreased with the length of the follow-up to just over 60%, and was comparable in both groups (Fig. 1). The mean persistence with the treatment was 35.5 weeks for the control group and 36.1 weeks for the intervention group (P>0.05). The studied groups differed significantly in their level of adherence: the average MPR (± SD) was 95.4 ± 53.7% for the intervention group, and 81.7% ± 31.0% for the control group (P<0.05). In the control group, MPR reached higher values among the elderly (92.0 ± 22.7% among patients aged 65 and over) compared with the younger ones (78.2 ± 32.7%, P<0.05). No other significant MPR differences were observed according to gender or age in either of the groups studied, nor for the total studied population.

In both groups a systematic decrease in total cholesterol (Fig. 2), LDL-cholesterol, and triglycerides, with a relatively constant level of HDL-cholesterol, was observed. At the end of 48-week follow-up period, studied groups did not differ in their values of any of the above-mentioned parameters (P> 0.05).

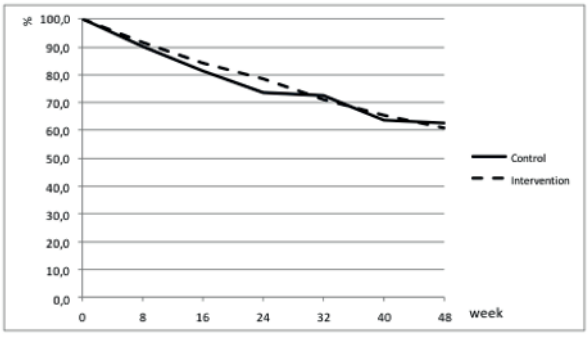

Figure 1. The rate of patients continuing statin therapy over time, by study group.

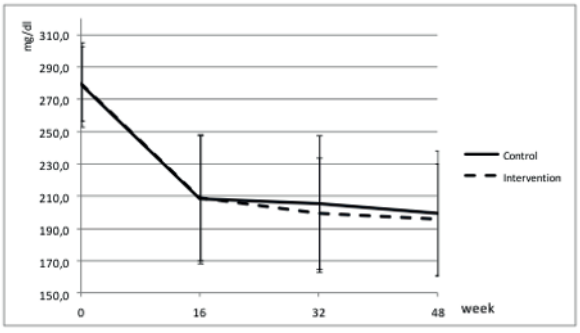

Figure 2. Changes of total cholesterol level over time, by studied group.

Adverse effects occurred in 20.7% of the total studied patients, with similar frequency in both groups (respectively, 22.4% in the intervention group, and 18.7% in the control group, P>0.05). Most frequently these were mild symptoms from the gastrointestinal tract, in the form of heartburn, stomach or abdominal pain (7 subjects, that is 3.5% of the studied population). In neither of the studied groups patient adherence, expressed by MPR, was significantly correlated with either presence or absence of adverse effects.

4. Discussion

Non-adherence is one of the major barriers to the development of modern medicine. It accounts for significantly lowered effectiveness of treatment carried out in the conditions of everyday clinical practice, compared with therapy in the strictly controlled conditions of clinical trials. As a result, despite the availability of evidence-based therapies, a significant portion of outpatients does not achieve reachable benefits of treatment.

Numerous determinants of patient adherence have been identified so far [16]. Chronic nature of the disease and the consequent need for life-long treatment, asymptomatic nature of the disease, and the lack of

direct noticeable effects of the therapy are having negative impact on adherence [17]. All these factors converge in the case of hyperlipidemia. Given the high prevalence of this disease in Poland [18], and the scale of its health and economic consequences, ensuring high level of adherence to lipid-lowering medication is an important need. However, an analysis of pharmacy claims in the southwest of Poland revealed that only 12% of patients had adhered to their statin treatment, taking at least 80% of recommended doses [19]. This highlights the need for developing effective interventions to improve patient adherence to lipid lowering treatment. However, a meta-analysis of available literature proved that the currently available methods to improve adherence are mostly complex, and their effectiveness is only limited [20]. Starting from this assumption, our study was designed to assess the effectiveness of the inexpensive and relatively simple intervention, combining educational (information materials distributed to patients) and behavioural part (adopting a routine activity designed to remind of the necessity to take a medicine). This intervention has lead to a substantial improvement in adherence, as expressed by MPR.

Our results are consistent with findings of the recent publications. For example, a nurse-led cardiovascular risk-factor counseling composed of providing patients with personalized risk assessment, and highlighting individual modifiable risk factors, had positive effect on both adherence to statins, and lipids level in primary prevention patients [21]. Intervention composed of in-hospital counselling, attention to adherence barriers, communication of discharge medications to community pharmacists and physicians, and ongoing assessment of adherence by community pharmacists had a positive effect on adherence to statins in secondary prevention patients [22]. The pharmaceutical care programs resulted in lower rates of discontinuation within initial period of statin therapy [23,24]. Patient support and reminders were also found to be the most effective out of 4 categories of intervention (simplification of treatment regimen, patient education, patient support and reminders, and complex behavioural approach) in a recently published systematic review [25].

On the other hand, to author's knowledge, the behavioural element of intervention, used in this study, that is adopting a routine activity reminding about the necessity to take the medicine, has not been previously used in interventions aimed at improving adherence to lipid lowering treatment. Its role is even greater considering that simvastatin, the drug used in this trial, like other statins, is a type of medicine that should be taken in the evening. This fact implies the risk of non-adherence in the form of missing single doses, despite the requirement of taking just one dose daily, as the evening doses used to be taken by patients less systematically than the morning ones [26].

However, when interpreting the results of this study one needs to be aware of its limitations. These include the single-centre nature of the study and a limited number of studied subjects. Also, the study did not take into account if the enrolled patients were treated with simvastatin in primary or secondary prevention, although the inclusion criteria - limited to treatment-naive cases of hyperlipidemia - indirectly favoured primary prevention. Available data show that discontinuation of lipid lowering treatment is more frequent in primary prevention than in the secondary one [27]. The methodology employed to assess adherence in this study, that is the assessment of the number of prescriptions and time of their issuing, and not their realisation, resulted from the lack of nationwide electronic prescription system in Poland, a situation that does not allow for tracing of realisation of individual prescriptions by individual patient. This however may change in the nearest future, with expected implementation of the e-prescription system. Finally, the lack of impact of tested intervention on lipid parameters can be linked to the fact that the sample size was calculated for primary outcome measure, ie. adherence to medication.

Despite these limitations, the results of this study may have high practical use. Improvement in adherence achieved through educational and behavioural interventions may indeed lead to a higher effectiveness for treatment of hyperlipidemia, more effective prevention of its complications, and indirectly - to reducing cardiovascular morbidity, and mortality. Noteworthy, better adherence to lipid-lowering treatment was observed to reduce healthcare costs, despite increased drug spending [28]. Therefore, implementation of tested intervention may be expected to lower costs of the healthcare system, with obvious benefits for public health. Finally, findings of this study may be used to design similar strategies to improve adherence in the other chronic conditions, and especially asymptomatic ones, such as hypertension, or diabetes type 2.

5. Conclusions

Simple, affordable educational and behavioural intervention proved effective in improving patient adherence to statins in the outpatient setting, as expressed by medication possession ratio. This effect was particularly noticeable in those aged below 65. Given that the benefits of lipid lowering treatment, achieved by pa-

tients, are proportional to the degree of their adherence to treatment; and the tested interventions is relatively inexpensive and easy to implement in clinical practice; these results may have a large impact on clinical and economic outcomes.

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