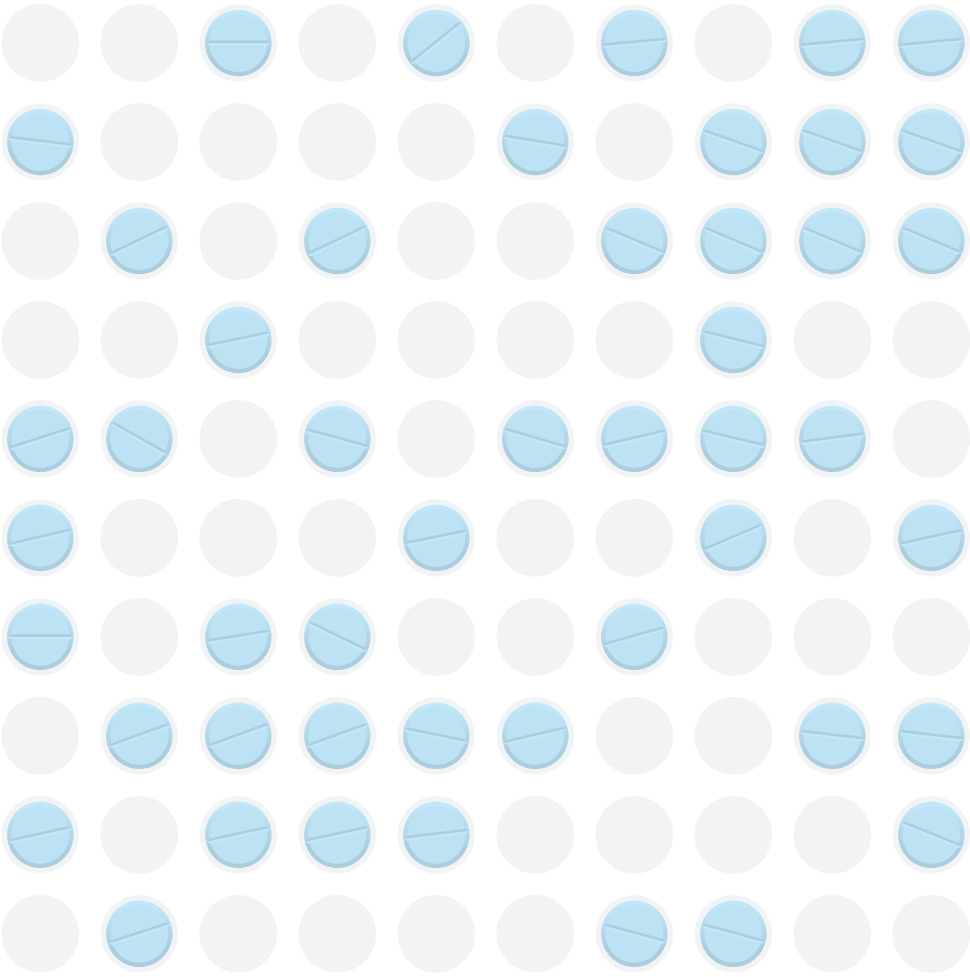

Medication Adherence in Chronic Pain Patients

Leon Timmerman

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CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Chronic pain

Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 months).[1] Pain is a unique, individual and subjective experience that encompasses biological, psychological, and social factors. According to the World Health Organization, chronic pain is a chronic disease in its own right. Its prevalence is reported to be one in five adults around the world.[2-4] Chronic pain is a major source of personal suffering, including a negative impact on quality of life, sleeping and functionality.[2] Furthermore, it constitutes a major economic burden for society. In the United States alone, the economic costs associated with chronic pain were estimated in 2010 to be between $ 560-635 billion annually.[5]

Like other chronic diseases, chronic non-malignant pain is managed primarily in primary care, where it accounts for 20% of all patients evaluated. Only 5% of these patients reported having ever consulted a pain specialist.[6] The treatment of chronic pain is challenging, and a considerable amount of patients report poor outcome.[2,7] Chronic pain treatment frequently requires a multidisciplinary 'bio-psycho-social' approach, including physical rehabilitation and psychological support. However, pharmacotherapy is one of the cornerstones of pain therapy.[8] Analgesic medications are on top of the list of classes of drugs prescribed during physician consultations or emergency room visits.[6] However, the effects of pain medication on chronic pain are variable and often not as good as desired. Placebo-controlled outcome studies for pharmacological approaches to chronic pain reveal that they provide, on average, a meager 30% efficacy.[9] The numbers-needed-to-treat (NNT) with the most effective monotherapy to achieve pain reduction of at least 50% are in the range of 2 to 4 meaning that on the average one patient in 2 to 4 has his/her pain halved.[9] Several factors may account for the variable effects of pain treatment, including age, pharmacokinetic differences and pharmaco-genetic variability.[10]

Medication non-adherence

Another reason for the sub-optimal effect of chronic pain treatment may be that patients do not adhere to the prescription of the care provider. Adherence can be defined as "the extent to which a person's behaviour corresponds with the agreed recommendations from a health care provider".[11] Poor medication adherence is relatively common. Studies in chronic conditions have shown consistently that 20 to 30 percent of medication prescriptions are never filled and that, on average, 50 percent of medications for chronic disease are not taken as prescribed. In developing countries, the rates are even higher.[11] Non-adherence is a complex multifactorial behaviour. Determinants include patient-related, provider-related and healthcare system-related factors.[12] Unintentional non-adherence, e.g. due to inability to schedule, administer or remember the treatment, is mostly related to the lack of patients' capacity or resources

to adhere to prescribed therapy. Intentional adherence is a conscious decision that involves patient perception of necessity and concerns about prescribed therapy. Non-adherence to chronic therapy in general leads to poor health outcomes and increased health care costs.[12,13] The price of nonadherence is considerable. In the United States, estimated direct and indirect costs totaled $ 337 billion in 2013 due to otherwise-preventable hospital admissions, emergency room visits, physician visits and medical tests.[13]

The prevalence of non-adherence to chronic pain therapy has been reported to be considerable as well: 30 percent of patients used less medication, and 14 percent took more medication than prescribed.[14] Underuse and overuse of medication are two separate patterns of non-adherence that should be differentiated, as they have different causes and consequences. Non-adherence to chronic pain medication has been associated with reduced treatment effects.[15,16] Although a causal relation has not been established, it seems plausible that 'drugs don't work in patients not taking them'.[17] Furthermore, overuse of pain medication can inevitably lead to health care risks or even death.

Apart from overuse of pain medication with an intention to control pain symptoms, opioid abuse and addiction to prescribed pain medications have been described to have reached epidemic proportions. Nearly half of all U.S. opioid overdose deaths involve a prescription opioid. In 2015, more than 15,000 people died there from overdoses involving prescription opioids.[18] Abuse and addiction have been classified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[19] They are considered separate entities from medication non-adherence, with separate risk factors and management strategies.[20] However, the line between overuse on the one hand, and abuse or addiction on the other, may be thin.[14]

Interventions

The World Health Organization recognizes a definite need for action to improve medication adherence: "*Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments*".[11] As medication adherence is typically the result of a combination of patient, provider, health care system and policy factors, most of the effective interventions for chronic conditions in general were indeed multifactorial: over half were aimed at multiple targets and most had multiple components.[21] In other words, no single "silver bullet" exists for medication adherence. Studies identifying the active ingredients of these complex interventions are lacking, making it difficult to reproduce them in clinical practice. In chronic pain management, there were no studies reporting successful interventions up to now.

AIMS AND CONTENTS OF THIS THESIS

The aim of the work presented in this thesis was to explore the concept of medication adherence in chronic non-malignant pain patients in order to design effective interventions to improve pain medication adherence.

Chapter 2 describes a systematic literature review of the prevalence and determinants of medication non-adherence.

Chapter 3 presents the results of a prospective correlational study investigating the relationship between knowledge and medication adherence in chronic non-malignant pain patients.

In **chapter 4**, the results of a randomized clinical trial investigating the effect of a standardized medication-specific information video on pain medication adherence and treatment outcome are reported.

Chapter 5 describes the results of a randomized clinical trial investigating the effect of three follow-up strategies on medication adherence and treatment outcome.

Chapter 6 reports on the associations between patients' beliefs about pain medication, medication adherence patterns and outcome parameters.

Chapter 7 presents the design of a theory-based adherence improving intervention using the COM-B model of behaviour.

Chapter 8 discusses the main findings, addresses the study limitations, and considers various implications for daily practice and future research.

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CHAPTER 2

Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review.

Leon Timmerman
Dirk L Stronks
George Groeneweg
Frank J.P.M. Huygen

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ABSTRACT

Background

Chronic pain is commonly treated with analgesic medication. Non-adherence to prescribed pain medication is very common and may result in suboptimal treatment outcome. The aim of this review is to investigate the prevalence of medication non-adherence and to present determinants that may help identify patients at risk for non-adherence to analgesic medication.

Methods

A search was performed in PubMed and Embase with systematic approach including PRISMA recommendations. Individual risk of bias was assessed and systematic data extraction was performed.

Results

Twenty-five studies were included. Non-adherence rates to pain prescriptions ranged from 8 to 62 percent with a weighted mean of 40 percent. Underuse of pain medication was more common than overuse in most studies. Factors that were commonly positively associated with non-adherence were dosing frequency, polymedication, pain intensity, and concerns about pain medication. Factors negatively associated with non-adherence were age, again pain intensity and quality of the patient-caregiver relationship. Underuse was positively associated with active coping strategies and self-medication, and negatively associated with perceived need for analgesic medication. Overuse was positively associated with perceived need, pain intensity, opioid use, number of prescribed analgesics, a history of drug abuse and smoking.

Conclusion

Non-adherence to analgesic medication is very common in the chronic pain population. The choice for pharmacological therapy should not only be based upon pain diagnosis, but should also take the risks of non-adherence into account. The value of adherence monitoring or adherence enhancing interventions has to be investigated in future studies.

INTRODUCTION

Non-adherence to chronic medical therapy is reported to play a substantial role in the sub-optimal efficacy of chronic disease treatments.[1,2] Medication adherence in chronic disease, i.e. diabetes, hypertension, COPD and mental health care, has been studied extensively. In these populations, non-adherence to medication resulted in increased health care costs, morbidity and mortality.[3] A meta-analysis of 569 studies reported an average non-adherence rate across diseases of 20,6%.[3] Determinants of non-compliance as well as successful interventions have been presented to improve compliance and treatment outcome.[2,4-10]

In chronic pain, there is a growing interest for the impact of non-adherence to pharmacological pain treatment as well. Chronic non-malignant pain is a common health problem that leads to disability as well as high medical and societal costs. Although chronic pain requires a multidisciplinary approach, pharmacological therapy remains a cornerstone of chronic pain treatment. Whereas over 60% of pain sufferers use medication to relieve their pain, this therapy is often not as effective as desired.[11] Adherence research in chronic pain management has, due to increasing reports of prescription drug abuse, been primarily focused on identification and prevention of opioid overuse, abuse and addiction.[12, 13] This is due to the epidemic increase in prescription drug abuse and addiction problems since the 1990s, mostly described in North America. However, addiction and abuse, with their own recognized risk factors, should be considered phenomena different from non-adherence. Abuse has a more compulsory character and deals with other issues than medication adherence. With regard to adherence, most deviations from physician instructions are omissions, i.e. underuse of medications.[14,15] In a previous review, a mean of 29,9% of chronic non-malignant pain patients took less medication and 13,7% took more medication than prescribed.[16] Although it seems obvious that drugs will not be effective in patients not taking them, it is still unknown whether improvement of medication adherence will result in improved outcome in chronic pain patients. Awareness of the incidence of non-adherence and knowledge of determinants of non-adherence may help prescribing caregivers to make decisions about pain treatments and follow-up strategies. The aim of this review is to provide an update on the prevalence of medication non-adherence in chronic non-malignant pain patients and to present determinants that may help identify patients at risk for non-adherence to analgesic medication.

METHODS

This review was conducted according to a predefined protocol containing inclusion criteria, outcome parameters and a data collection chart. The protocol has not been registered in a review database. Study selection, data extraction and quality assessment was performed by

two reviewers (LT and DLS) independently. Discrepancies were discussed until consensus was reached.

Literature search

We performed a literature search using Pubmed and Embase databases. We completed the database search on October 13, 2014. The keywords used in the Pubmed database were: (adherence OR compliance OR misuse) AND chronic pain AND (medication OR drug). The search strategy in Embase was as follows: chronic pain'/exp OR 'chronic pain' AND (adherence:ab,ti OR compliance:ab,ti OR misuse ab,ti). Two independent reviewers screened citations and abstracts for relevance. Full text articles of relevant citations were retrieved and judged according to the inclusion criteria. Reference lists were screened for additional papers. If there was any doubt regarding the inclusion of a paper, the study was discussed until consensus was reached.

Eligibility criteria

We included original reports of studies that described pain medication non-adherence in chronic non-malignant pain patients aged 18 years and older as an outcome measure quantitatively. Retrospective, prospective and cross-sectional studies in English, German and Dutch literature were assessed for inclusion, regardless of their publication status. Articles reporting adherence to analgesics qualitatively were excluded in the study. Articles were also excluded if they reported adherence to anti-rheumatic medication that was primarily focused on modifying disease activity. Studies focusing on aberrant opioid taking behavior including substance abuse, diversion, and illicit drug use without describing actual medication adherence quantitatively were excluded. Furthermore, reports describing the analyses of large databases of urine samples or pharmacy records instead of patient populations were excluded as well.

Data extraction

Duplicate data extraction was performed using a standardized checklist containing the following variables: study design, year of publication, sample size, population, definition of adherence, method of measuring adherence, non-adherence level and determinants associated with non-adherence. If a determinant was shown to be associated with adherence in one or more studies, other studies were screened for conflicting results (no association found) regarding this determinant. Finally, funding sources and conflicts of interest reported in the included studies were recorded.

Quality assessment

The methodological quality of the eligible studies was assessed at study level using an assessment list based on recommendations from Sanderson, Tatt and Higgins.[17] This quality assessment checklist has been designed for use in observational adherence research and contains 11 items concerning selection methods, measurement of variables, sources of bias, control

for confounding and appropriate use of statistics (Table 1).[18] Given the fact that the results almost entirely concern longitudinal relationships between predictive factors and adherence (for which the Sanderson et al criteria were designed) we decided to use this list for quality assessment for all the studies, including the prospective studies and randomized trials. Two observers assessed the quality of the studies independently, and discrepancies were discussed

Table 1. Quality assessment checklist for observational adherence studies constructed by Pasma et al.. Bold items indicate the 'essential criteria'.

Appropriate methods for patient selection

1 Positive if the main features of the study population are described (sampling frame and distribution of the population by age and sex)

2 Positive if the participation is >80% or if participation is 60–80% and non-response is not elective (data presented)

Methods for Measuring Exposure and Outcome Variables

3 Positive if method for measuring adherence is reproducible

4 Positive if method for measuring adherence is valid (blood serum/urine measurements, MEMS, pharmacy records and a validated questionnaire are considered valid, patient questionnaire and/or interviews and healthcare provider assessment are considered as not valid)

5 Positive if method for measuring determinants is reproducible

Appropriate Design-Specific Sources of Bias

6 Was serious recall bias reduced? (adherence <1 week)

7 Was serious selection bias reduced? (by inviting consecutive patients/ representative sample)

Appropriate Methods to Control Confounding

8 Positive if the analysis is controlled for confounding (such as age/sex) or effect modification

9 Positive if the effect of confounding is quantified in analysis (univariate and multivariate analysis)

Appropriate Statistical Methods (Primary Analysis of Effect but Excluding Confounding)

10 Positive if quantitative measures of association are presented (such as r, β, OR), including 95% CI's and numbers in the analysis(totals)

11 Positive if the number of cases in the multivariate analysis is at least 10 times the number of independent variables in the analysis (final model)

and resolved. Each item answered with 'yes' received one point. Five items were considered as essential questions. Studies were considered to be of high quality if 4 out of 5 of the essential questions were answered with 'yes' and if the total score was 7 or higher.

RESULTS

The reviewing process is presented in figure 1. The Pubmed and Embase search retrieved 2803 and 3990 citations, respectively. Eighty full-text articles were retrieved, 25 articles were included in this review.[14, 19-42] Most articles were excluded because they focused on opioid abuse. The design and method of adherence measurement of the included studies are shown

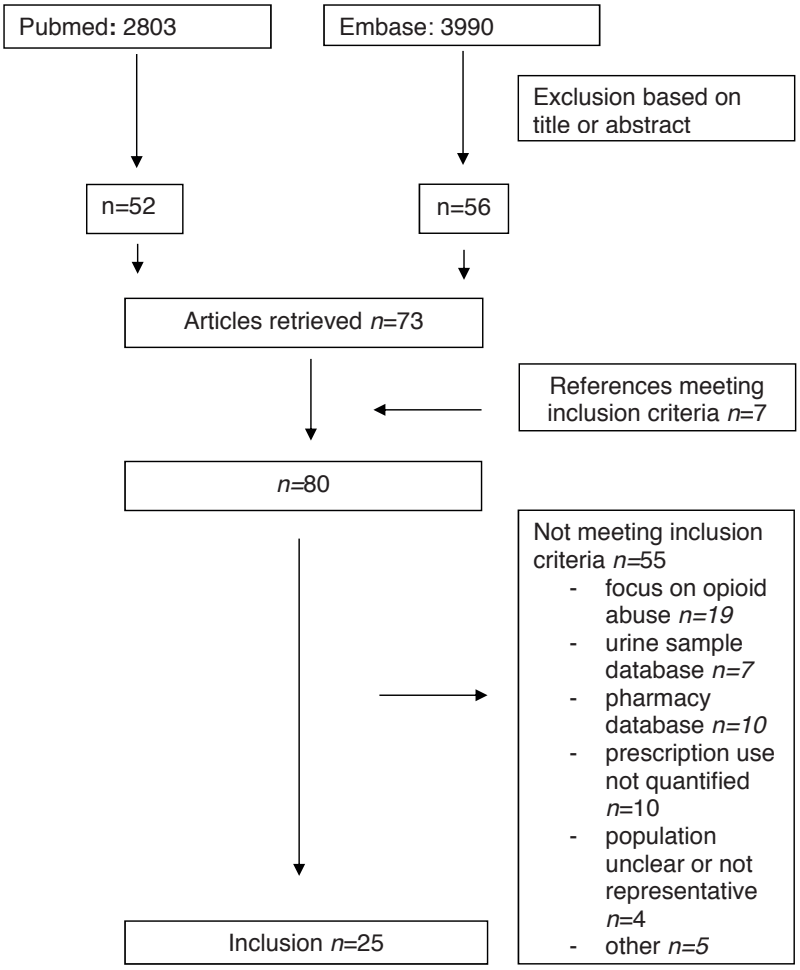

Fig. 1. Flow chart of study selection.

in table 2. Self-report was most frequently used to measure adherence, followed by structured interview, electronic monitoring, and urine screening, respectively (Table 2). Nine studies were performed in a population with chronic non-malignant pain in general [21,27,31-34,36,39,40], nine studies focused on chronic pain patients using opioids [14,25,26,30,35,37,38,41,42], two studies focused on chronic headache or migraine [19,23], two studies included patients with rheumatic diseases (ankylosing spondylitis, osteoarthritis) [20,22], two studies concerned fibromyalgia [24,28] and one study concerned patients with diabetic neuropathy using SSRIs or gabapentin treatment (table 3).[29]

Table 2. Study characteristics.

Author	Year	Design	N	Adherence measurement
Packard [19]	1986	Prospective descriptive study	88	Interview
Weinberger [20]	1991	Randomized clinical trial	439	Self report
Berndt [21]	1993	Prospective correlational study	99	Urine screening
De Klerk [22]	1996	Randomized controlled trial	65	MEMS
Mulleners [23]	1998	Prospective observational study	29	MEMS
Sewitch [24]	2004	Prospective correlational study	127	Self report (MMAS-4)
Manchikanti [25]	2005	prospective comparative study	200	Urine screening
Ives [26]	2006	Prospective cohort study	196	Urine screening/ pharmacy records
McCracken [27]	2006	Cross sectional correlational study	220	Self report
Dobkin [28]	2006	Prospective correlational study	121	Self report (MMAS-4)
Giannopoulos [29]	2007	Randomized clinical trial	93	Interview and pill count, SSRI or gabapentin prescribed
Navato [30]	2009	Prospective observational study	105	Urine screening
Lewis [14]	2010	Cross sectional correlational study	191	Structured interview
Broekmans [31]	2010	Cross sectional correlational study	281	Structured interview
Broekmans [32]	2010	Cross sectional correlational study	265	Self report
Nicklas [33]	2010	Cross sectional correlational study	217	Self report (medication adherence report scale)
Stern [34]	2011	Cross sectional correlational study	1321	Self report (missed dose previous week)
Chang [35]	2011	Cross sectional correlational study	21	Self report (MMAS-8)
Rosser [36]	2011	Cross sectional correlational study	239	Self report (four questions)
Bronstein [37]	2011	Prospective observational study	41	Urine screening
Grattan [38]	2012	Cross sectional study	1191	Structured interview
Timmerman [39]	2013	Prospective observational study	96	Structured interview
Markotic [40]	2013	Cross sectional correlational study	100	Self report (direct questioning and MMAS-4)
Barth [41]	2014	Cross sectional study	307	Self report
Mattelliano [42]	2014	Retrospective study	120	Urine screening

Table 3. Prevalence of non-adherence to pain medication in chronic pain patients.

Author	Year	Population	Non-adherence (%)			Definition	Comments	
			G	U	O			
Packard	1986	headache	52			Non-adherence: Not taking medication as prescribed, alcoholism or drug abuse.	Non-adherence at second follow-up visit: 38,6%.	Self report or structured interview: any deviation considered as non-adherence
Weinberger	1991	osteoarthritis		33		Non-adherence: report of missing a single dose or more.	33,4% follow up 11 months	
Berndt	1993	chronic non-malignant pain	23	2	21	Adherence: take medication as prescribed, and reliable report of additional medication.	Underuse 2%; overuse 21%; 10% unknown, 32% difference urine toxicology and self report.	
McCracken	2006	chronic non-malignant pain	37			None-adherence: medication taken less often, more often, or at a different dose.		
Lewis	2010	CNCP opioid users	29	20	9	Overuse: Taking more than the dosage allowed by the prescription. Underuse: Taking less than allowed by the prescription AND report inadequate pain relief.	Underuse: 20% Overuse 9%	
Broekmans[32]	2010	chronic non-malignant pain	48	32	14	Non-adherence: any deviation from prescription	Underuse 32%; overuse 14%; both 2%	
Broekmans[33]	2010	chronic non-malignant pain	62	40	14	Non-adherence: any deviation from prescription	Underuse 40%; overuse 14%; both 8%	
Stern	2011	chronic non-malignant pain		34		Adherence: not having missed a single dose in the previous week.	According to physician: 19,6%	
Grattan	2012	Chronic opioid use, no history substance abuse			51	Overuse: Taking more than the dosage allowed by the prescription. Misuse: opioid use for other than pain symptoms. Aberrant behaviour: giving opioids to or getting them from others.	Underuse not reported Overuse: 51% Misuse: 43% Aberrant behaviour:17%	
Timmerman	2013	chronic non-malignant pain	58			Non-adherence: any deviation from the prescribed therapy the day before adherence measurement.		
Markotic	2013	chronic non-malignant pain in patients aged > 65	57			Direct questioning: do you take your prescription exactly as prescribed? (yes/no);	MMAS-4: 16% high adherence, 43% medium adherence, 41% low adherence	Self-report: MMAS
Sewitch	2004	fibromyalgia		47		Non-adherence: one positive answer on MMAS-4.		
Dobkin	2006	fibromyalgia		53		Non-adherence: one positive answer on MMAS-4.		
Chang	2011	chronic non-malignant pain in older adults, opioids prescribed	57	47	11	Higher scores MMAS-8 indicate better adherence.	Underuse 47%; overuse 10%	

Table 3. Prevalence of non-adherence to pain medication in chronic pain patients. (*continued*)

Author	Year	Population	Non-adherence (%)			Definition	Comments	
			G	U	O			
Nicklas	2010	chronic non-malignant pain	25			Admitting non-adherent behavior on one or more questions of the Medication Adherence Report Scale (MARS).		Self-report: Other Questions
Rosser	2011	chronic non-malignant pain	38	45	27	Four questions, two related to underuse and two related to overuse, were answered on a five-point scale.	Underuse 44,8%; overuse 26,9%	
Barth	2014	Chronic pancreatitis, opioid users.	39			Non-adherence: Current Opioid Misuse Measure (COMM) positive for misuse		
De Klerk	1996	ankylosing Spondylitis	22			Adherence: percentage of *days* on which dose taken as prescribed (MEMS)		MEMS
Mulleners	1998	migraine	33			Adherence: correct number of openings MEMS	9,2% using pill count / 56% not on schedule	
Giannopoulos	2007	painful diabetic neuropathy		12		Non-adherence: receiving less than 75% of scheduled dosages	Definition more liberal than other studies	Pill count
Manchikanti	2005	CNCP opioid users		32		UDT negative for prescribed drug	Underuse 32%; non-prescribed opioid 7%; illicit drugs 23%	
Ives	2006	CNCP opioid users		8		UDT negative for prescribed drug	Underuse 7,6%; non-adherence including diversion, prescription forgery and multiple providers 32%	
Navato	2009	CNCP opioid users		50		UDT negative for prescribed drug	Non-adherence 68%: - Absence of drug: 50% - Positive for illicit drugs: 24% - Other medications: 48%	Urine screening
Bronstein	2011	CNCP, opioids prescribed		41		UDT negative for prescribed drug; levels inconsistent with prescribed dosage	Non-adherence: 41% Illicit substance: 5%	
Matteliano	2014	CPP opioid prescribed		23		UDT negative for prescribed drug or inappropriate level prescribed substance	Abnormal UDT: 54% - Absence of drug: 23% - Other non-prescribed drug: 12,5% - Marijuana 24,2%; cocaine 11,7%	

Prevalence

The reported rates of non-adherence in patients with chronic pain, including the definition used for non-adherence, are shown in table 3. Non-adherence rates ranged from 8 % to 62 % with a weighted mean of 40%. Six of the studies made clear distinction between medication under- and overuse.[14,21,31,32,35,36] In most of these latter studies, underuse was more common than overuse.[14,31,32,35,36] Another five studies only investigated underuse non-adherence.[20,24,28,29,34] From five studies measuring adherence by urine screening, only prescription underuse rates were used in this review. Rates of non-prescribed or illicit drug use, or other aberrant drug taking behaviors in these studies were disregarded.[25,26,30,37,42] One large study only measured opioid overuse.[38] Underuse of medication ranged from 2% to 53% with a weighted mean of 33%. Overuse ranged from 9 to 51% with a weighted mean of 33%, considering that the mean overuse rate was largely increased by a single large study on opioid overuse.[38]

Determinants

Nineteen studies were found to describe determinants of medication adherence of chronic non- malignant pain patients (Table 4). Factors most frequently mentioned as positive predictors of non-adherence were higher dosing frequency, polypharmacy and low but also high pain intensity, followed by younger age, concerns about pain medication, and an unsatisfactory patient-caregiver relationship. Four studies made a clear distinction between determinants of medication underuse and –overuse.[27,31,32,36] Underuse was associated positively with concerns about side effects and addiction, and negatively with concerns about withdrawal and perceived need for analgesic medication.[27,36] Active coping strategies and self-medication were also described to be positively associated with underuse as well.[31,32] Overuse was associated positively with perceived need, pain intensity, opioid use, a history of drug abuse, smoking and a number of prescribed analgesics.[27,31,32,38]

We divided the factors predicting non-adherence into the five categories, as described by the World Health Organization:

1. Socio-economic factors

Educational level was negatively associated with analgesic adherence in one study.[33] Two studies did not find this association.[32,39]

2. Health care team and –system related factors

Difficulties in the therapeutic relationship, defined as mistrust in the doctor or discordance in communication and satisfaction, were negatively associated with adherence.[24,27,36] Medication underuse was related to lack of information provided in the hospital.[32]

Table 4. Determinants of medication adherence to pain medication in chronic pain patients

Author	Year	N	Determinants of non-adherence	Comments
Berndt	1993	99	Polymedication, history of drug abuse	
Mulleners	1998	29	Higher dosing frequency	Article described medication prophylaxis instead of symptomatic treatment
De Klerk	2002	127	Symptom modifying instead of disease controlling drug, higher dosing frequency, male sex Better perceived health, coping patterns (avoidance related to lower compliance; expression of emotions and passive reaction pattern related to better adherence)	
Sewitch	2004	127	Unintentional: community subjects, lower disease activity, less use of instrumental coping, higher discordance on communication and satisfaction, not under rheumatologist's care for more than a year. Intentional: not under rheumatologist's care <1 year, higher discordance on communication and satisfaction. Overall: higher discordance on communication and satisfaction	
Dobkin	2006	121	Lower affective pain ratings, higher psychological distress	
McCracken	2006	220	Overall: lower pain intensity, mistrust in doctor, concern over addiction Underuse: higher pain intensity, concern over side effects, less concerns over withdrawal, less perceived need Overuse: higher pain intensity, perceived need, concern over scrutiny	
Manchikanti	2005	200	Long acting opioids did **not** improve adherence	
Ives	2006	196	Younger age, drug or DUI conviction, history of cocaine or alcohol abuse	
Grattan	2012	1334	Misuse: depression Opioid use for non-pain symptoms: male sex, lower daily dose, less education Overuse: higher pain intensity Overuse and aberrant behavior: younger age Aberrant behavior: white race, less education, lower daily dose	
Barth	2014	307	Depression, high pain intensity, impaired psychological quality of life, alcohol use	
Matteliano	2014	120	Age, pain level, sex, ethnicity, injury compensation did **not** predict aberrant drug taking behavior	
Giannopoulos	2007	93	Patients on SSRIs were more compliant than patients on gabapentin	
Nicklas	2010	217	Adherence and Illness perceptions Questionnaire: perceptions of illness as chronic, uncontrollable and unremitting were more adherent. Adherence and beliefs about medication: higher concerns were less adherent, higher necessity were more adherent Age, pain level and educational level positive correlation with adherence	
Broekmans [32]	2010	281	Underuse: younger age, more use of (non-prescribed) self-medication Overuse: younger age, higher dose frequency, opioids prescribed, smoking	
Broekmans [33]	2010	265	Underuse: higher number of prescribed analgesics, self-medication, lower pain intensity, active coping, lack of information, side effects Overuse: higher number of prescribed analgesics, smoking Overall: higher number of prescribed analgesics, prescription of non-opioids	
Rosser	2011	239	Overall: mistrust in doctor, concerns about side effects, less concern over withdrawal Underuse: lower level of pain, mistrust in doctor, less concern over withdrawal Overuse: perceived need, concerns about side effects	
Stern	2011	1351	Higher pain intensity	
Markotic	2013	100	Higher number of analgesics or other drugs, fear of addiction, side effects, belief that sleepiness due to analgesics is bothersome, higher pain intensity.	
Timmerman	2013	96	Less knowledge of the prescription, higher age	

3. Condition related factors

Pain intensity was positively associated with adherence.[27,29,33] More specifically, underuse was associated with lower pain intensity [32,36] and overuse with higher pain intensities.[27,38,41] On the other hand, pain intensity was negatively associated with adherence in one study [40] and underuse was associated with higher pain intensity in two studies [27,34]. One study reported no association between pain level and medication adherence.[42]

4. Therapy related factors

Polymedication and higher dosing frequency were negatively associated with adherence.[21-23,31,32,40] In two studies, compliance was associated with the type of medication prescribed, i.e., patients on SSRI" s were more compliant than patients on gabapentin.[22,29] The use of opioids was described to correlate with overuse.[31] Long acting opioids were described not to improve adherence, compared to short acting opioids.[25]

5. Patients related factors

Age was positively associated with analgesic adherence.[26,31,33,38] One study described a negative association [39] and two studies reported no association between medication adherence and age.[32,42] Perceptions of illness were reported to predict adherence, as patients that considered their illness as chronic, uncontrollable and unremitting were more adherent.[22,33] Patients that used active coping strategies and self-medication to improve their symptoms were underusing their analgesics more often.[31,32] Knowledge of prescribed pain medication was positively related to adherence to this prescription.[39]

Attitudes and concerns towards pain medication were reported to predict adherence.[27,33,36,40] Perceived need for pain medication was associated with overuse, less perceived need was associated with underuse.[27,36] Concerns about addiction, adverse scrutiny and tolerance were positively associated with a general measure of non-adherence, whereas concerns about side effects and little concerns about withdrawal symptoms correlated with prescription underuse.[27,36,40] Psychological distress positively predicted non-adherence in two studies.[29,41] A history of drug abuse [21,26] as well as smoking [31,32] predicted overuse non-adherence.

Quality assessment

Thirteen of the 25 selected studies were of high methodological quality (Table 5).[21,22,25-27,31,32,34,38-42] Although 17 studies fulfilled 7 out of 11 methodological criteria, 4 of these studies did not meet 4 of the essential criteria. Twelve studies did not use a validated measure of medication adherence, mostly self-report. Validated measures included urine screening, Medication Event Monitoring System (MEMS), Current Opioid Misuse Measure (COMM) and both versions of the Morisky Medication Adherence Scale: 4 questions (MMAS-4) or 8 questions (MMAS-8).

Table 5. Results of the quality appraisal with the quality assessment checklist.

References	Selection methods		Measurement of study variables			Sources of bias		Control of confounding		Use of statistics		Score
Question	1	2	3	4	5	6	7	8	9	10	11	
Markotic	y	y	y	y	y	n	y	y	y	y	y	**10**
Barth	y	y	y	y	y	dk	y	y	y	y	y	**10**
De Klerk	y	n	y	y	y	y	y	y	y	y	y	**10**
Grattan	y	y	y	n	y	y	y	y	y	y	y	**10**
Stern	y	y	y	n	y	y	y	y	y	y	y	**10**
Broekmans (2)	y	y	y	n	y	y	y	y	y	y	y	**10**
Ives	y	y	y	n	y	y	n	y	y	y	y	**10**
Broekmans (1)	y	y	y	n	y	y	dk	y	y	y	y	**9**
Timmerman	y	y	y	n	y	y	n	y	y	y	y	**9**
McCracken	y	y	y	n	y	n	y	y	y	y	y	**9**
Sewitch	y	dk	y	y	y	n	y	y	y	y	y	9
Berndt	y	dk	y	y	y	y	y	y	n	n	y	**8**
Manchikanti	y	y	y	y	y	y	y	y	n	n	na	**8**
Rosser	y	n	y	y	y	n	n	y	y	y	y	8
Nicklas	y	n	y	n	y	n	y	y	y	y	y	8
Dobkin	y	dk	y	y	y	n	n	y	y	y	y	8
Mattelliano	y	na	y	y	y	y	y	n	n	y	na	**7**
Giannopoulos	y	dk	y	n	y	y	dk	y	n	y	na	6
Chang	y	dk	y	y	y	y	n	n	n	y	na	6
Mulleners	y	dk	y	y	y	y	dk	n	n	y	na	6
Navato	y	y	y	y	na	y	dk	na	na	n	na	5
Bronstein	n	y	y	y	na	y	y	na	na	n	na	5
Weinberger	y	n	y	n	y	y	n	y	n	n	na	5
Lewis	y	n	n	n	y	dk	n	na	na	n	na	2
Packard	y	dk	n	n	n	n	y	na	na	n	na	2

Bold scores indicate high-quality studies. y, yes; n, no; na, not applicable; dk, don't know.

Conflicts of interest

Six studies reported funding by internal or external research grants.[14,22,27,28,35,38] Conflicts of interest were declared in three reports.[34,37,42] Stern and colleagues are employees of Grunenthal Pharma SA.[34] Bronstein declared to be employee at the medical affairs department of Ameritox, a company that provides urine drug tests.[37] Mattelliano reported to be an educational speaker at Millenium laboratories, a company that provides urine drug tests.

DISCUSSION

Non-adherence to prescribed analgesic therapy is common in patients with chronic non-malignant pain, and might be one of the reasons that efficacy of medication in this population is limited.[34] A causal relationship between medication adherence and medication efficacy, however, has never been established in chronic pain management. As chronic pain is a complex, multifactorial disease, it is difficult to prove the importance of medication adherence, as the effect of analgesic therapy is generally limited.

Non-adherence to chronic disease treatment is generally associated with increased morbidity and mortality.[3] It is not known if the same holds true for adherence to symptomatic analgesic treatment in patients with chronic pain. At least, *assessment* of medication adherence is important to evaluate the ability of prescribed medication to control pain. We reviewed literature for the prevalence and determinants of non-adherence. We did not pool the data of studies because of the large differences in study design, studied populations, definitions of adherence, and methods of adherence measurement.

Prevalence

Pain medication non-adherence was common and generally more prevalent compared to non-adherence to other chronic disease treatments. In some chronic conditions, for example hypertension, non-adherence can be explained by the fact that there is no noticeable gain of medication. Although it seems obvious that ongoing pain and limitations motivates patients to take their medications correctly, adherence to symptomatic pain treatment has been described to be even worse than adherence to disease modifying drugs.[22]

Besides differences in pain diagnoses, the wide range of non-adherence rates may be explained by differences in defining and operationalizing non-adherence across the studies: *first*, although some studies in chronic-pain populations define non-adherence as any report of a missed dose or deviation of the prescription, other studies use more liberal definitions of adherence. Nevertheless, even in comparable studies with respect to population and adherence definition, large differences exist in the prevalence of non-adherence. *Second*, underuse and overuse non-adherence should be considered as two different entities with their own prevalence and determinants. However, most studies either focus on underuse or do not mention this distinction at all. Another explanation for the wide range of non-adherence rates may be that taking medication is in fact complex behavioral pattern, and whereas data on adherence are often reported as dichotomous variables (adherence vs. non-adherence), this might be an oversimplification of the subject.[15] Moreover, adherence can change in time, as it is a dynamic process. 'White coat adherence' is a phenomenon that has to be accounted for when interpreting study results: patients may follow prescriptions better just before and after a follow-up visit.[43] Finally, several methods were used to measure medication adherence. Subjective methods (self-report and a structured interview), using validated questionnaires or simple

questioning were most frequently used. They are easy to apply and inexpensive. Unfortunately, they tend to overestimate compliance.[44] Objective methods are generally more reliable for monitoring adherence. A Medication Event Monitoring System (MEMS), an electronic pillbox which records pill box openings, is an example of objective adherence monitoring. Although it is used as an adherence monitor, patients are aware of being monitored, and MEMS may partly be considered as an adherence intervention. Urine analysis is widely used to monitor adherence, especially in patients on chronic opioid therapy. It is reliable to detect prescription drugs and illicit substances qualitatively. Quantitative measurements are less reliable because of inter-individual differences in metabolism.[45] Therefore, patients overusing their medication, mostly opioid users, will not be identified by urine testing alone. Other methods to measure compliance with treatment regimens are pill count, or calculation of the medication possession ratio (MPR), which requires a closed pharmacy system.[15] Each method has its advantages and pitfalls. At this point, patient interview remains the most practical approach for clinicians, while a combination of adherence measures seems to be optimal for research purposes.[46]

Determinants

The choice for a specific therapeutic regimen might influence adherence behavior. Poly-medication and higher dosing frequency may negatively influence adherence, and a higher number of analgesics is associated with underuse of prescribed therapy.[21-23,31,32,40] Therefore, it may be beneficial to limit the number of analgesic prescriptions in patients at risk for non-adherence. However, although the effect of once day dosing schedules on adherence has been shown, the effect on outcome has not been established. Chronic pain patients that sense the effect of each individual dose might prefer more daily dosing as a way to keep control over their symptoms.

The type of medication prescribed may play a role in the patterns of medication use.

Overuse was more prevalent in, but not limited to, patients taking opioids. Grattan et al. described in their large study that half of the patients taking opioids were overusing their medications. Most important reasons for this are the strong and relatively fast mode of analgesic action of opioids (*noticeable gain*), and the existence of opioid dependency, abuse or addiction. In one study, patients with diabetic neuropathy were more adherent to antidepressant (SSRIs) than to anticonvulsant (gabapentin) therapy.[29] Another study that was excluded for this review confirmed these findings. [47] This could possibly be explained by the fact that SSRIs are better tolerated and that they are dosed, unlike gabapentin, once a day.

Unfortunately, most pain medications cause side effects. Surprisingly, the presence of side effects was related to non-adherence in only two studies.[32,40] Most side effects occur at the beginning of the therapy, and unacceptable side effect will be followed by a dose reduction or change of therapy. Therefore, non-adherence due to side effects will be missed in a more stable treatment regimen in which patients were seen in most studies reviewed.

Beliefs about illness and beliefs about medication are important predictors of adherence behavior.[27,33,36] Perceptions of illness as chronic, uncontrollable and unremitting were reported to

predict adherence positively.[33] To increase the likelihood of adequate adherence it is important that perceptions of necessity of analgesic therapy outweigh specific concerns regarding the prescription.

The caregiver-patient relationship has been mentioned in three studies as an important determinant of non-adherence.[24,27,36] The consultation itself plays an important role, as the relationship between physician and patient will be built here. Providing adequate information, shared decision making and proposing a treatment plan with feasible goals may ensure a positive patient-physician relationship without mistrust. Furthermore, attitudes and concerns towards illness and medication can be addressed in this consultation, and alternative treatment options can be proposed.[14, 27,36] Patients have to realize that they carry responsibility for the success of their treatment as well, and they should be actively involved and motivated.[48]

Adherence and treatment outcome

In chronic pain, there is no consensual standard for what constitutes adequate adherence. As it is symptomatic treatment, it might not be justified to label non-adherence as 'incorrect' behavior automatically. In some serious chronic conditions such as HIV-infection, strict adherence is mandatory for positive treatment outcome. In chronic pain, some deviation from the prescription may be acceptable without serious consequences for treatment efficacy. In fact, as described above, a causal relationship between adherence and pain reduction has never been shown for chronic pain treatment until now. The relationship between adherence and outcome is even more complex, as 'good outcome' is not well defined. Some patients prefer other outcomes than pain reduction, e.g., the ability to drive a car or having no side effect of prescribed medications.

Pain intensity has been associated with adherence in both directions. If there is little or no pain, patients may feel pain medication unnecessary. High pain levels may be interpreted as a higher need for pain medication, and may therefore lead to better adherence or even overuse of pain medication. On the other hand, patients who do not use their medications may have higher pain intensities than patients that use their prescription correctly. Adherence to medication is also thought to improve outcome by mechanisms other than the actual effects of medication. In one study on B-blocker use, adherence to placebo was strongly associated with mortality.[49] The authors concluded that, while probably not due to publication bias or simple confounding by healthy lifestyle factors, the underlying explanation for the association remained 'a mystery'. Adherence itself might be seen as a measure of, or proxy for, other positive behavioural properties that are beneficial for people with HTN or pain.

Predicting non-adherence in general practice

When considering prescription of pain medication, the risk of non-adherence should be considered. Several efforts have been made, especially in the field of opioid prescribing, to stratify patients into risk categories. Questionnaires as the Prescription Drug Use Questionnaire (PDUQ),

Diagnosis Intractability Risk and Efficacy Score (DIRE) and the Pain Medication Questionnaire (PMQ) have been developed to predict aberrant opioid taking behavior.[12, 50-52]

Non-adherence to pain medication might be anticipated by identifying risk factors for non-adherence as described above, including younger age, polymedication, negative attitudes or concerns towards the use of medication, psychological distress and a history of drug abuse. Patient at risk might benefit adherence improving interventions or alternate therapy.

Interventions

Interventions that improved medication adherence are mostly described in other chronic conditions: simplification of the medication regimen, patient education, behavioral interventions (reminders, encouragement), SMS-reminders and eHealth-interventions.[2,4-10] Interventions to improve non-intentional non-adherence, for example SMS reminders, may be more easily implemented than interventions for intentional non-adherence in a chronic pain population. Improvement of intentional non-adherence might need a more patient tailored intervention targeted at determinants of inadequate medication use.

Regular follow-up and monitoring for adherence monitoring have been shown to improve medication-taking behavior in chronic opioid therapy.[53,54] In the American literature, in which opioid abuse is predominantly described to be a serious and extensive national health problem, routine drug testing during opioid therapy is advocated.[54,55] In chronic non-opioid pain therapy, only one intervention was studied without significant effect on medication adherence.[20]

Limitations

The results of this review were partly based on studies of limited methodological quality. However, half of the studies were of high quality, and results of low quality studies generally confirmed findings of high quality studies regarding non-adherence rates and determinants of non-adherence. The main limitation of this study is the heterogeneity of the studies reviewed with respect to definition of adherence, adherence measurement, study design and pain diagnoses. Focusing on a smaller subset of studies would have led to insufficient data for an update on this subject. Furthermore, as our literature search was limited to two databases, and our search criteria did not include specific diagnoses, we might have missed relevant records in this review. Nevertheless, we assume to have provided a representative overview of current literature on the topic of pain medication adherence.

CONCLUSION

In conclusion, the number of publications on prevalence and determinants on medication non-adherence in chronic non-malignant pain patients has increased in the last decade. Medication non-adherence in chronic pain patients is common, and factors predicting non-adherence

have been presented. Despite this, there is still no evidence for the importance of adherence on pain reduction. Future studies should investigate if, and to what extent, medication adherence is actually important for pain treatment outcome. The actual prescription of pain medication should be part of a larger treatment plan including non-adherence risk stratification, information, shared decisions about treatment strategy and adequate follow-up including monitoring of medication use. Possibly, additional interventions as reminders, patient education or eHealth applications might play a role, but their role has to be evaluated in future studies.

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CHAPTER 3

Adherence to pharmacological pain therapy in patients with non-malignant pain: the role of patients' knowledge of pain medication

Leon Timmerman
Rudolf Stellema
Dirk L. Stronks
George Groeneweg
Frank J.P.M. Huygen

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ABSTRACT

Background

Non-adherence to pharmacological therapy is a common and underexposed problem in chronic non-malignant pain patients. It may lead to treatment failure and increased health care costs.

Methods

In this prospective observational study we analysed the association between knowledge and adherence in the chronic non-malignant pain population. We included 96 patients treated with a new pharmacological prescription. During the initial visit (T0) demographic variables, pain intensity, knowledge of the prescription (name, dose and frequency), self-reported adherence to the prescription and general knowledge of pharmacological pain therapy (according to the Pain Knowledge Questionnaire, Dutch Language Version (PKQ-DLV)) were recorded. During two follow-up visits (T1, T2), apart from demographics, these parameters were measured again.

Results

Adherence rates were 42%, 42% and 46% at T0, T1 and T2, respectively. 53%, 59% and 48% of patients had knowledge of their current prescription, and mean scores on the PKQ-DLV were 56, 55 and 52 percent of the maximum scores, respectively at T0, T1 and T2. A multivariate binary logistic regression analysis resulted in a significant contribution of knowledge of the prescription and of age to the prediction of adherence.

Conclusions

Knowledge of the analgesic prescription is associated with adherence and significantly contributes to the prediction of adherence to analgesic therapy. An interventional study is needed to determine whether increasing knowledge will improve medication adherence and therapy outcome in chronic non-malignant pain patients.

INTRODUCTION

Chronic non-malignant pain is a common health problem that leads to disability as well as high medical and societal costs. Although over 60% of pain sufferers use medication to relieve their pain, this therapy is often not effective. Non-adherence to the prescription is reported to play a major role in the sub-optimal effect of chronic pharmacological therapy.[1] The prevailing definition of adherence is 'the extent to which a person's behaviour (in terms of taking medication, following diets, or executing lifestyle changes) coincides with medical or health advice'.[2] Broekmans et al. reported that in patients with chronic non-malignant pain, non-adherence is common: 29.9% (range 2-53%) of the patients used less medication and 13.7% (range 3-21%) used more medication than prescribed.[3]

Non-adherence to prescribed analgesics is an underexposed problem in chronic pain management. For other chronic conditions (e.g. HIV infection, asthma, diabetes and cardiovascular disease) much more is known about the prevalence and determinants of non-adherence and interventions to improve adherence.[1,2,4] In general, poor adherence to medication accounts for a substantial worsening of disease, readmissions to the hospital, death, and increased healthcare costs.[5] Recently, it has been shown that adherence to prescribed medication is negatively associated with pain intensity.[6] However, it is still unknown whether a causal relationship exists between adherence and the outcome of chronic pain therapy. In some serious chronic conditions such as HIV-infection, strict adherence is mandatory for positive treatment outcome.[7] In chronic pain management, some deviation from the prescription may be acceptable without serious consequences for treatment efficacy.

Knowledge of determinants of medication adherence contributes to the prediction and identification of non-adherent behaviour in clinical practice. Furthermore, understanding why, when and which patients are non-adherent is essential for developing strategies to improve medication taking behaviour. Adherence research in chronic pain management has, due to increasing reports of prescription medication abuse, been primarily focused on identification and prevention of opioid overuse and abuse.[8,9] However, most deviations from physician instructions are omissions, i.e. underuse of medications.[5] Determinants of medication underuse that are reported in chronic pain management include age, psychological distress, poor communication with providers, lower affective pain ratings, poor clinical attendance [3], active coping strategies and use of self medication.[10] Furthermore, patients' concerns and beliefs about the prescribed therapy play an important role in their medication taking behaviour.[11-13]

Knowledge of the disease or the prescribed therapy was found to be positively correlated to medication adherence in other conditions, and patient education was successfully used to improve adherence.[14-17] The present study investigates the association between knowledge and adherence to a pharmacological prescription in patients with chronic non-malignant pain.

METHODS

Design

Our study was a prospective observational study.

Patients

Included were consenting outpatients with chronic non-malignant pain persisting for at least 3 months, who were treated with a new pharmacological pain prescription at the Center of Pain Medicine of the Erasmus Medical Center. Patients had to be aged ≥18 years and have adequate understanding of the Dutch language. Excluded from the study were patients receiving pain medication on an 'as needed' basis.

Measurements

Measurements were made during the first visit to our Center of Pain Medicine (T0), and during two consecutive follow-up visits after one (T1) and three months (T2), respectively. Patients underwent a structured interview by study personnel not involved in clinical care of the study participants. At T0 measurements included: demographic variables (age, gender, educational level); medical variables (location and duration of pain, mean pain intensity in the previous week using an 11-point numeric rating scale [18]) and medication adherence: the prescribed pain therapy was compared with the anamnestic use of medication the day before measurement: 'which pain medication(s) did you use yesterday?'. Knowledge of the prescription was determined by asking for the name, dose and frequency of the therapy prescribed and comparing the result with the actual prescription as noted in the patient file. In addition, general knowledge on the pharmacological pain therapy was evaluated using a Dutch language version of Ferrell's Patient Pain Questionnaire.[19] This questionnaire consists of eight statements that could be answered on a five point Likert-scale (strongly agree, agree, not agree/not disagree, disagree, strongly disagree). For ease of interpretation, all item scores were linearly transformed to a 0-100 scale and a total score was computer for overall pain knowledge. This Pain Knowledge Questionnaire (PKQ-DLV) was translated backward and forward and pretested in a group of 49 chronic cancer pain patients. It demonstrated acceptable levels of validity and reliability.[20]

At T1 and T2, apart from demographics, location and duration of the pain, all the aforementioned parameters were measured again. Knowledge of the prescription and adherence to it were assessed using to the current pharmacological pain therapy.

Data analysis

Adherence to prescribed therapy was determined by recording adherence to: the drug, the dose of the drug, and the frequency of the prescribed dose regimen. Any deviation regarding the type, dose or frequency of medication in relation to the prescribed therapy was defined as non-adherence. Overall adherence was defined as adherence at T1 and T2 to all three aspects

mentioned above. Knowledge of the name, dose and frequency was recorded dichotomously and overall knowledge was defined as knowledge at T1 and T2 of all three aspects. T0 was left out of the analysis because knowledge measured at T0 concerned knowledge of the newly prescribed medication (and not knowledge of earlier prescribed therapy as at T1 and T2).

Item scores of the PKQ-DLV were linearly transformed to a 0-100 scale, after recoding five items, and a total score was computed for general pain knowledge.

Statistical analysis

Descriptive statistics were used to determine frequencies. Binary logistic regression analysis was used to evaluate the contribution of parameters to the prediction of adherence to the prescribed medication. To prevent overfitting of the model, we performed univariate binary logistic regression analyses of demographic parameters (gender, age and education), overall knowledge of the prescription, general knowledge of pharmacological pain therapy at T0, and pain intensity in the previous week at T0. Only those parameters with a significance level of $p \leq 0.2$ were entered into the final multivariate stepwise binary logistic regression analysis (method Backward Wald) with a probability out of p=0.1. To prevent multicollinearity, pairwise correlations between the parameters to be entered into the final model were calculated. Of those with a bivariate correlation of ≥ 0.7 only the parameter with the highest univariate significance level was entered into the final model. Analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 16.0.

RESULTS

Demographics

Of the 112 patients initially included in the study, 17 later declined to participate.

At T0, T1 and T2 a total of 95, 88 and 79 patients, respectively, participated in the study. At T0 there were 30 (31.6%) male and 65 (68.4%) female participants with a mean age of 52.5 (SD 15.1) years; details of their educational level are given in Table 1. In the week prior to T0, mean pain intensity was 7.8 (SD 1.5). At T0, 62 patients were unemployed (65.3%), 27 of them (43.5%) due to functional disability.

Table 1. Level of education at T0 according to the International Standard Classification of Education (1997).

	n (%)
None	2 (2.4)
Primary education	12 (14.5)
Lower secondary education	44 (53.0)
Upper secondary education	14 (16.8)
Tertiary education	11(13.3)
Total[1]	83 (100)

[1] Data of 12 patients are missing.

Medication

Table 2 lists the analgesic therapy of patients before and after their first visit to the Center of Pain Medicine. Of all patients, 25% did not use any medication at all before their initial visit.

Co-analgesics (antidepressants and anticonvulsants) were prescribed more frequently at the Center than in earlier therapy, and therapy with sedatives and hypnotics was rarely prescribed.

Table 2. Analgesic therapy before and after the first visit to the Center of Pain medicine.

	Medication before treatment (n (%))	Medication after treatment (n (%))
Step 1 WHO ladder	54 (57.4)	19 (20.2)
Step 2 WHO ladder	31 (33.0)	10 (10.6)
Step 3 WHO ladder	12 (12.8)	6 (6.4)
Anticonvulsants	15 (16.0)	24 (25.5)
Antidepressants	12 (12.8)	20 (21.3)
Anti-migraine medication	2 (2.1)	0
Hypnotics, sedatives, anxiolytic medication	18 (19.1)	1 (1.1)
Sympathicolytic medication	1 (1.1)	1 (1.1)
Muscle relaxants	3 (3.2)	0
Topical medication	1 (1.1)	0
Vasodilator therapy	1 (1.1)	2 (2.1)
Other	3 (3.2)	1 (1.1)
Unknown	4 (4.3)	28 (29.8)
No analgesic therapy	25 (26.6)	0
Total[1]	182 (193.6)	112 (119.1)

[1]Data of 1 patient are missing. Total score exceeds 100%, indicating that some patients used more than one analgesic drug.

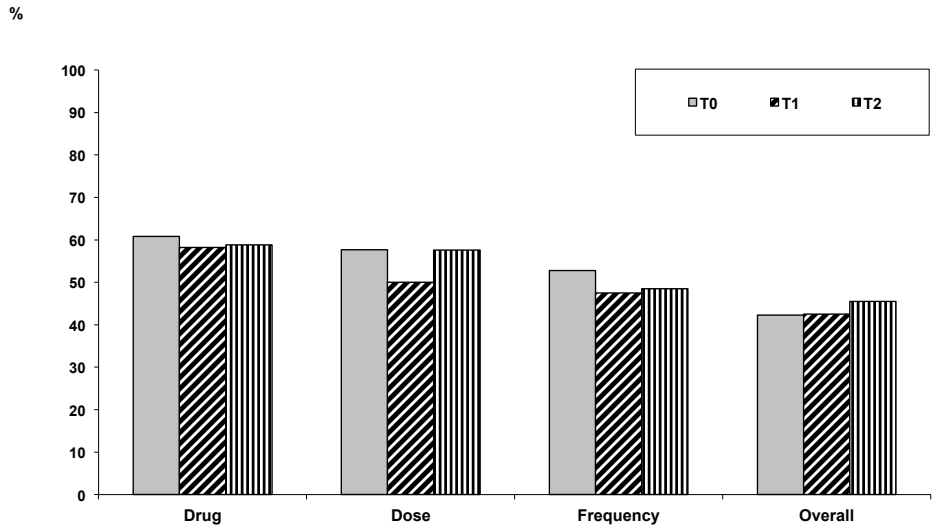

Figure 1. Percentage of patients adherent to the drug, dose and frequency of the prescription, and the combination of these three aspects (overall adherence).

Medication Adherence

Figure 1 shows the proportion of patients that were adherent to the prescribed pain therapy during the study period. Overall adherence to the prescription is 42, 42 and 46 percent at T0, T1 and T2, respectively. Adherence to single aspects of the prescription was only slightly higher. There were no significant differences between the different aspects of adherence (adherence to drug, dose, frequency). There was no significant difference between measurements at T0, T1 and T2.

General knowledge of analgesic therapy

Table 3 presents data on general knowledge of pharmacological pain therapy. The lowest level of knowledge concerned the question '*In analgesic therapy, it is important to use the lowest possible dose. Higher doses can then be reserved for more severe complaints*'. The

Table 3. General knowledge on analgesic therapy according to the PKQ-DLV. Data are shown as mean scores (SD) on the eight questions on pain therapy. Higher scores indicate better pain knowledge.

	T0	T1	T2
Pain can be treated effectively.	52.6 (30.4)[a,b]	60.8 (29.8) [a]	56.6 (31.4) [b]
Pain therapy should only be considered in case of severe pain. [c]	49.7 (39.0)	45.2 (41.3)	42.4 (35.9)
Most patients who use analgesic medication will develop some sort of addiction over time. [c]	43.2 (32.1)	37.2 (34.1)	39.2 (33.9)
In analgesic therapy it is important to use the lowest dose possible. Higher doses can then be reserved for more severe complaints. [c]	36.3 (41.9) [a,b]	27.3 (36.1) [b]	15.2 (26.4) [a,b]
It is advised to use analgesic therapy on a regular basis, instead of dosing on an 'as needed' basis.	80.3 (30.3)	79.3 (33.3)	78.5 (33.7)
There are other ways to treat pain besides analgesic medication.	66.6 (31.7)	71.0 (31.0)	70.6 (31.2)
Too many patients receive too much analgesic medication. [c]	40.8 (34.0)	43.2 (35.9)	41.8 (34.1)
I can easily change the prescribed analgesic regimen myself, without consulting my doctor. [c]	70.8 (38.2)	72.4 (35.0)	67.4 (38.3)
Total score	55.9 (14.4) [a,b]	54.8 (16.1) [b]	51.7 (14.2) [a,b]

[a,b] Significant difference between groups are indicated by identical superscripts ($p<0.05$).
[c] Items were recoded

Knowledge of the prescription

Figure 2 shows the proportion of participants that had knowledge of the specific aspects of their analgesic prescription. About 50% of the patients had overall knowledge on the different aspects of their prescription during the study period. There were no significant differences between the different aspects of the prescription, or between the measurements at T0, T1 and T2.

Logistic regression analysis

The univariate binary logistic regression analyses revealed that only overall knowledge of the prescription ($p=0.01$), general knowledge of pharmacological pain therapy ($p=0.05$) and age ($p=0.08$) significantly contributed to the prediction of adherence.

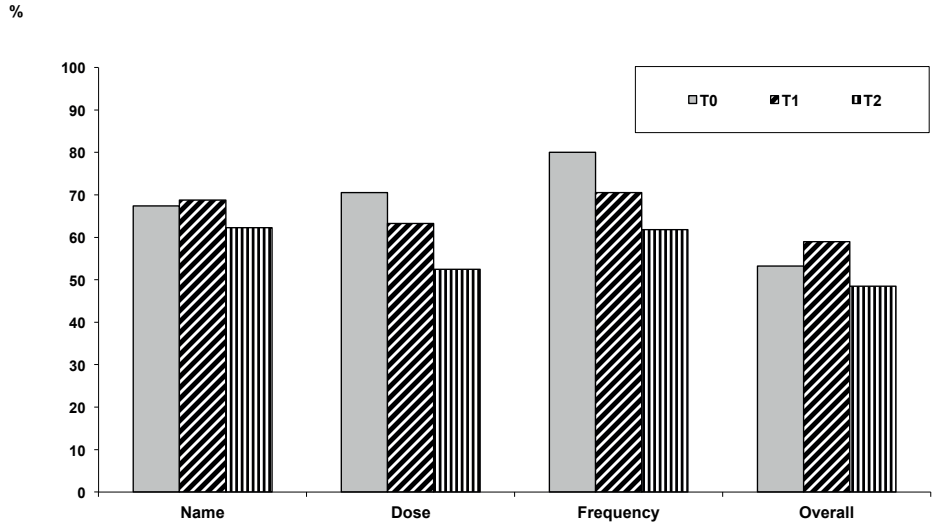

Figure 2. Percentage of patients with knowledge on the different aspects and overall knowledge of the prescription.

Entering the above-mentioned parameters into the final multivariate binary logistic regression analysis resulted in a significant contribution of overall knowledge of the prescription and of age (Table 4). The sensitivity (71.4%), specificity (70.6%), and overall classification (70.8%) were high. A cut-off value of 0.24 was used.

Table 4. Results of the multivariate binary logistic regression analysis.

		95% CI for Odds Ratio		
Included	B (SE) [p-value]	Lower	Odds Ratio	Upper
Constant	2.05 (1.68) [0.22]			
Age	- 0.08(0.04) [0.02]	0.86	0.92	0.99
Knowledge	2.09 (0.04) [0.02]	1.73	8.05	37.51

DISCUSSION

Whether strict adherence is necessary to optimize outcome of pharmacological pain therapy, is unknown. In chronic pain, some deviation from the prescription may be acceptable.

Nevertheless, as *'drugs don't work in patients who don't take them',* awareness of medication-taking behaviour is important when assessing the effect of prescribed therapy. In our chronic non-malignant pain sample, although mean pain intensities were high, adherence to prescribed analgesic therapy was low. During the 3-month study period ≤ 50 percent of the patients were adherent. Other studies measuring self reported adherence reported comparable high levels of non-adherence.[21-23] The selected method of measuring adherence, i.e. self-report, can be

susceptible to misinterpretation as patients often overestimate their compliance to prescribed therapy.[5] For this reason, it is unlikely that this method is responsible for the low levels of adherence found in this and earlier studies.[11,23] We defined every single deviation from the prescribed therapy as non-adherent behaviour. This strict definition, which is used in most adherence research in chronic pain, may partly account for the high levels of non-adherence found in this and other studies. Medication adherence is difficult to operationalize, firstly because it is not a dichotomous variable but varies from 0 to more than 100% as people may overuse their medications.[5] Secondly, it is a dynamic process, as it can change over time. We measured adherence the day before their visit, but this does not guarantee the same level of adherence on other days. 'White coat adherence' is a phenomenon that has to be accounted for when interpreting the results: patients may follow prescriptions better just before and after a follow-up visit.[24]

In the present study, about 50% of the patients had no knowledge of one or more aspects of the medical prescription. The regression analysis showed a significant relationship between knowledge of and adherence to prescribed analgesic therapy. To depict the association between overall knowledge of the prescription and adherence, we performed a post-hoc univariate analysis. Of those who were adherent, the proportion of patients with overall knowledge of the prescription (compared to those who had not) was found to differ substantially; this difference was significant ($p < 0.02$, Fisher's Exact test) (Fig. 3). Of those patients who did not know the name, dose or frequency of their analgesic regimen, 86.1% was non-adherent compared to 54.2% of those who had this knowledge. In other words, patients who did not have knowledge of their prescription were significantly less adherent to their therapy.

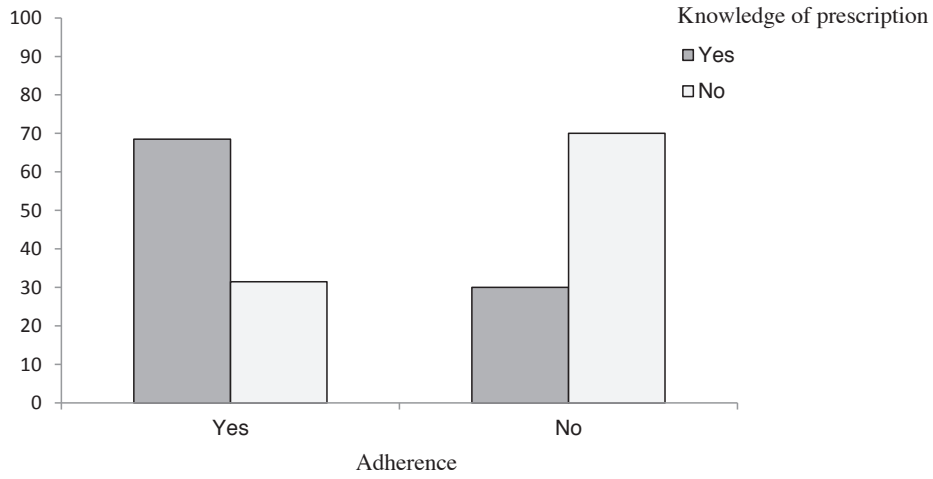

Figure 3. Percentage of patients with and without knowledge of their prescription in relation to adherence**.**

In this correlational study we cannot draw conclusions about the causality of the relationship between adherence and knowledge, but it seems plausible that knowledge of the prescription increases the chance of adherence to analgesic therapy. Asking for prescription details gives insight in the risk of non-adherence during clinical evaluation of a chronic pain patient. Even though it is possible to take medication correctly without knowing its' exact name or dose, it is more likely if these items are known to the patient. Furthermore, it is almost impossible not knowing the dosing frequency and still use medication properly. This emphasizes that health-care professionals should provide adequate information about the prescription. We defined knowledge of a prescription as knowledge of the name, dose and frequency. These basic items might not be the most important goals for an educational intervention. It seems unlikely that people who don't know which medication they actually use will have sufficient knowledge of important properties of the prescribed therapy. Experiences in other chronic conditions demonstrate that education on prescribed medication alone might be ineffective.[2,25] Communication should also address personal barriers and beliefs on pain medication, and education should focus on any specific concerns about prescribed medication.[13] When pain treatment is started in an informed patient by shared decision after concerns have been addressed, the patient may be more likely to adhere to the therapy.[12]

The results of the PKQ-DLV, in which only 56% of the maximum score was reached, suggest that basic knowledge on pharmacological pain therapy was low in this study population. The relationship between medication adherence and the results of the PKV-DLV was not significant in the final analysis. The PKV-DLV was designed and validated to test knowledge in cancer patients. Although non-malignant pain differs from cancer pain, it is assumed that the statements made on pain therapy can be used for non-malignant pain therapy as well. It has been used previously to test knowledge on non-malignant pain care in nurses [26], and the questionnaire appears suitable for use in a non-malignant pain population. Some statements, however, may not hold in this population, e.g. 'pain can be treated effectively'. In nurses and in cancer patients, an educational intervention positively affected the total PKQ-DLV score.[20,26]

Our study demonstrated a negative association between age and adherence. This might be the result of polymedication being more prevalent in older adults. Polymedication has been shown to be an independent risk factor for nonadherence.[27] Furthermore, decreased metabolism and excretion due to organ failure can increase the risk of adverse effects of medication in elderly patients, resulting in premature cessation of prescribed therapy. However, other studies reported a positive association between age and pain medication adherence. [28,29] These studies had a different design and performed adherence measurements in a more stable treatment phase, after initial dose finding had been performed. Psychological factors and active coping strategies, that are more prevalent in younger patients, are reported to predict non-adherence and may play a more important role after the initial treatment phase. [10,30,31]

In conclusion, the present study confirms that medication adherence of patients with chronic, non-malignant pain is low, with only about 50% complying with the prescribed therapy. In ad-

dition, knowledge of the prescription is low as well. Importantly, our study showed that knowledge of the prescription significantly contributes to the prediction of the level of adherence to analgesic therapy. This finding could be used as a tool to define the risk of non-adherence during evaluation of a chronic pain patient. Further study is needed to determine whether an educational intervention aimed at increasing knowledge of prescribed medication increases compliance with pain treatment and, most importantly, improves treatment outcome.

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CHAPTER 4

The value of medication-specific education on medication adherence and treatment outcome in patients with chronic pain: a randomized clinical trial.

Leon Timmerman
Dirk L. Stronks
George Groeneweg
Frank J.P.M. Huygen

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ABSTRACT

Objective

Non-adherence to pain medication is common and may jeopardize the effect of prescribed therapy in chronic pain patients. We investigated the effect of medication-specific education on pain medication adherence.

Methods

One hundred eligible chronic pain patients were randomized into a control or intervention group. They were assessed during an intake (T0) and two follow-up visits after 4 (T1) and 10 weeks (T2). Immediately after T1, patients in the intervention group additionally watched a video and received written information about the medication prescribed. At T1 and T2, medication adherence according to self-report including the Morisky Medication Adherence Scale, prescription knowledge, pain intensity (NRS), concerns about medication and patient satisfaction were recorded.

Results

Experimental group (control versus intervention) did not significantly contribute to the prediction of medication adherence at T2 ($p=0.38$). The non-adherence rates were 31 and 43 percent at T1 and 53 and 49 percent at T2 in the control and intervention group, respectively. Changes in patients' knowledge of the prescription were attributable to the intervention ($p<0.01$). No other significant differences were identified.

Conclusions

Medication-specific education did increase knowledge of the prescribed therapy but did not improve adherence or treatment outcome parameters. There was no association between medication adherence and pain treatment outcome.

INTRODUCTION

Chronic non-malignant pain is a common health problem that leads to disability as well as high medical and societal costs. Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans.[1] Although treatment requires a multidisciplinary approach, analgesic medication remains one of the cornerstones of the therapy. The response to drug treatment, which represents a complex interaction between analgesic medication and patient, is often poor and highly variable. There are several reasons for this variability. Age, gender, ethnicity and actual level of stress, mood or diseases may modify pain perception and pharmaco-genetic differences result in a variable response to pain medication.[2] Non-adherence to pain medication is also thought to play a role in the sub-optimal effect of analgesic therapy. Non-adherence to analgesics is very common and it seems plausible that medication will not work if it is not used properly.[3] However, patterns of adherence behavior are complex, especially in chronic pain patients, and may include underuse, overuse and abuse of pain medications. To predict and anticipate non-adherent behavior, risk factors for non-adherence should be addressed during consultation or, alternatively, by means of standardized checklists. Risk factors for non-adherence include younger age, complexity of the regimen, poly-medication, attitudes and concerns towards medication, low efficacy and side effects. Surprisingly, there are only few studies investigating interventions to improve medication adherence in the chronic pain patients.[4,5] In a previous study, we presented an association between knowledge of the prescribed medication, and medication adherence.[6] In this current study, we studied the effect of an educational intervention on medication adherence. The intervention consisted of a medication specific information video combined with written information. We chose to investigate this intervention for three reasons: first, we wanted to assess the effect of prescription knowledge improvement on medication adherence prospectively. Secondly, comparable medication videos, provided by pharmaceutical companies, are used in clinical practice already, although their effects on adherence and outcome are actually unknown. Finally, a short video might be a realistic intervention for routine use in clinical practice, particularly under the current pall of cost-containment and staff reductions. Knowledge of prescribed therapy, attitudes and concerns about pain medication and pain treatment outcome were studied as secondary outcome parameters.

METHODS

Participants

After approval by the Institutional Medical Ethical Review Board, a single-center randomized clinical trial was carried out at the pain treatment center of a large general hospital in the Netherlands. Patients at this pain treatment center are most commonly referred by general practitioners, neurologists, neurosurgeons or orthopedic surgeons. This study was performed

from August 2012 until July 2013. Patients were invited to participate in the study if they had received a new analgesic prescription from their pain physician and if they did not meet any of the exclusion criteria. We excluded patients aged younger than 18 years, patients who did not have the ability to speak and read the Dutch language, and patients who received medication on an 'as needed' basis. All participants provided written informed consent.

Study procedures

Patients, scheduled for an appointment at the pain treatment center, received written information about the study together with other routine documentation. All consecutive patients who received a new analgesic prescription were invited to participate directly after their appointment at the hospital by physician assistants who were not directly involved in patient care. After written informed consent, study questionnaires were completed by participants during three subsequent visits at the pain treatment center: directly after inclusion and before initiation of the newly prescribed medication (T0), directly before the first (T1) and second (T2) follow-up visit after 4 and 10 weeks, respectively. After the visit at T1, patients were randomized into two groups using a computer-generated sequence with a single block with a ratio of 1:1. Patients were assigned to receive either standard care (control group) or standard care with additional medication-specific information after the first follow-up visit (T1)(intervention group). Both groups received their usual consultations, with a scheduled duration of ten minutes, with a pain physician during all visits (standard care). Communication during these consultations was not limited nor controlled. The additional information in the intervention group consisted of viewing a 5-minute video in the hospital directly after the consultation. This video contained recordings of a pain physician providing standardized information about the medication prescribed: the name, frequently used dosing schedules, the type of medication (e.g. antidepressant, anticonvulsant), mode and speed of action and common side effects were discussed and presented in summarizing slides. Videos of the following prescriptions were available: pregabaline, gabapentin, oxycodone, fentanyl, amitriptylin, duloxetine and NSAIDs. When applicable, basic differences between nociceptive and neuropathic pain were explained. At the end of the video, patients were encouraged to contact the pain center in case of questions or problems. Furthermore, written medication-specific information about these topics was provided in the intervention group. The pain physician was not aware of the allocation of the patient.

Outcome measures

At T0, the following variables were collected: age, gender, level of education, mean and worst pain intensity in the preceding week (using an 11-point numeric rating scale (NRS)) and number of medications. At T1 and T2, the following variables were collected: knowledge of name, dose, dosing frequency and type of the medication (multiple choice question, e.g. antidepressant drug, opioid medication etc.) prescribed. Diagnoses were collected from the medical files after the study.

To increase reliability, we combined two separate self-report measures for medication adherence. First, both underuse and overuse were measured by self-report by asking how often the participant missed a dose or took additional medication, using a 6-point scale (0=never to 5=every day). When patients reported underuse, the reason was recorded (forgot to take medication, adverse effects, drugs don't work, pain under control, fear of addiction, other reason) to differentiate between intentional and unintentional nonadherence. The reason for overuse was recorded as well (accidentally, extreme pain, fear of withdrawal, other reason). Secondly, the 8-item Morisky Medication Adherence Scale (MMAS-8) consisting of 8 questions on medication adherence was used to measure pain medication underuse. It is a self-report measure originally designed to assess adherence to antihypertensive medications. It has good internal consistency (α=0.83) and concurrent and predictive validity.[7] MMAS may function as a screening tool in outpatient settings in other patient groups. Mean and worst pain intensity, perceived level of improvement (7-point scale: 0= worse than ever to 6= complete pain relief) and patient satisfaction (7 point scale: 0= absolutely dissatisfied to 6= absolutely satisfied) were recorded. Finally, the Pain Medication Adherence Questionnaire (PMAQ), a 47 -item questionnaire introduced by McCracken and colleagues, was completed.[8] The PMAQ assesses 7 areas of patient concerns: addiction, perceived need, scrutiny, adverse side effects, tolerance, mistrust in the prescribing doctor, and withdrawal. Items are rated on a 6-point numerical scale (0=never true to 5=always true); nine items are reversed; and the subscales are mean scores of relevant items. Internal consistency reliability for these subscales is adequate based on Cronbach's alpha values ranging from .77 to .85. Validity was demonstrated through significant predicted relations between the subscales and measures of medication use, disability, and emotional distress.[8]

Data analysis

Medication underuse was assessed by combining the results of both measurements of medication underuse described above. Underuse was defined as missing a dose once a week up to every day, regardless of pain intensity, and if they scored 2 or more positive questions on the MMAS. Medication overuse was defined as admitting to take any more medication than prescribed. General nonadherence was defined as presence of underuse and/or overuse of prescribed medication.

Knowledge of the prescription was calculated by counting the correct answers on the individual knowledge questions regarding name, dose, dosing frequency and type of medication, resulting in a minimum score of 0 and a maximum score of 4.

Statistical analysis

The *a priori* power analysis showed that a sample size of 80 was necessary to provide 80% power to detect a 10% change in adherence at α = .05; we planned to include patients until 96

patients were randomized to correct for missing data. Intention-to-treat analyses included all participants randomized.

Descriptive statistics were used to determine the frequencies of the demographic variables and the outcome parameters and to describe measures of central tendency and dispersion dependent on the shape of their distribution. The Kolmogorov-Smirnov test was used to analyze whether or not parameters were normally distributed.

Differences in proportions between the experimental groups at T0 were tested using the Fisher's Exact Test in case of dichotomous parameters or in all other cases the Pearson Chi square Test. Differences in continuous variables were evaluated using the Independent-Samples Mann-Whitney U test if the parameter was not normally distributed and the Independent-Samples T test if the parameter was normally distributed.

Binary logistic regression analysis was used to evaluate the contribution of the intervention to the prediction of adherence to the prescribed medication at T2 compared to the adherence at T1.

Differences in knowledge of and concerns towards the pain medication, pain intensities, perceived improvement, and patient's satisfaction between experimental groups over time (T1 to T2) were analyzed using multivariate repeated measures. Experimental Group and Time were the independent variables.

For the non-normally distributed variables we still decided to use multivariate analysis of variance (MANOVA) test. Although MANOVA test requires that each dependent variable entered into the analysis be normally distributed it was still used because the Monte Carlo experiments have shown that for sample sizes of 3 or 5 it is still possible to analyze leptokurtic, rectangular, J-shaped, moderately, and markedly skewed distributions. These experiments demonstrated that the empirically determined rejection region of the F-distribution would be no larger than $\alpha = 0.08$ when the usual 5% rejection is used.[9]

For all statistics, α was set at the traditional 0.05 level. All analyses were performed using IBM SPSS Statistics version 21. (SPSS, Inc, Chicago, IL).

RESULTS

Study sample

In the period between August 2012 and July 2013, 123 patients were invited to participate, 120 patients were included and 100 patients were randomized in this study (Figure 1). After informed consent, 2 patients withdrew their consent at T0. At T1, 18 additional patients were either lost in follow-up (6), received non-medication therapy (10) or withdrew their consent (2), leaving 100 patients to be randomized. At T2, 8 additional patients did not respond to the questionnaires due to loss in follow-up (4) or withdrawal of consent (4), leaving 92 patients that provided complete primary outcome data. Analyses were performed using data from these 92 patients. The 47-item PMAQ was completed without omissions by 81 patients only.

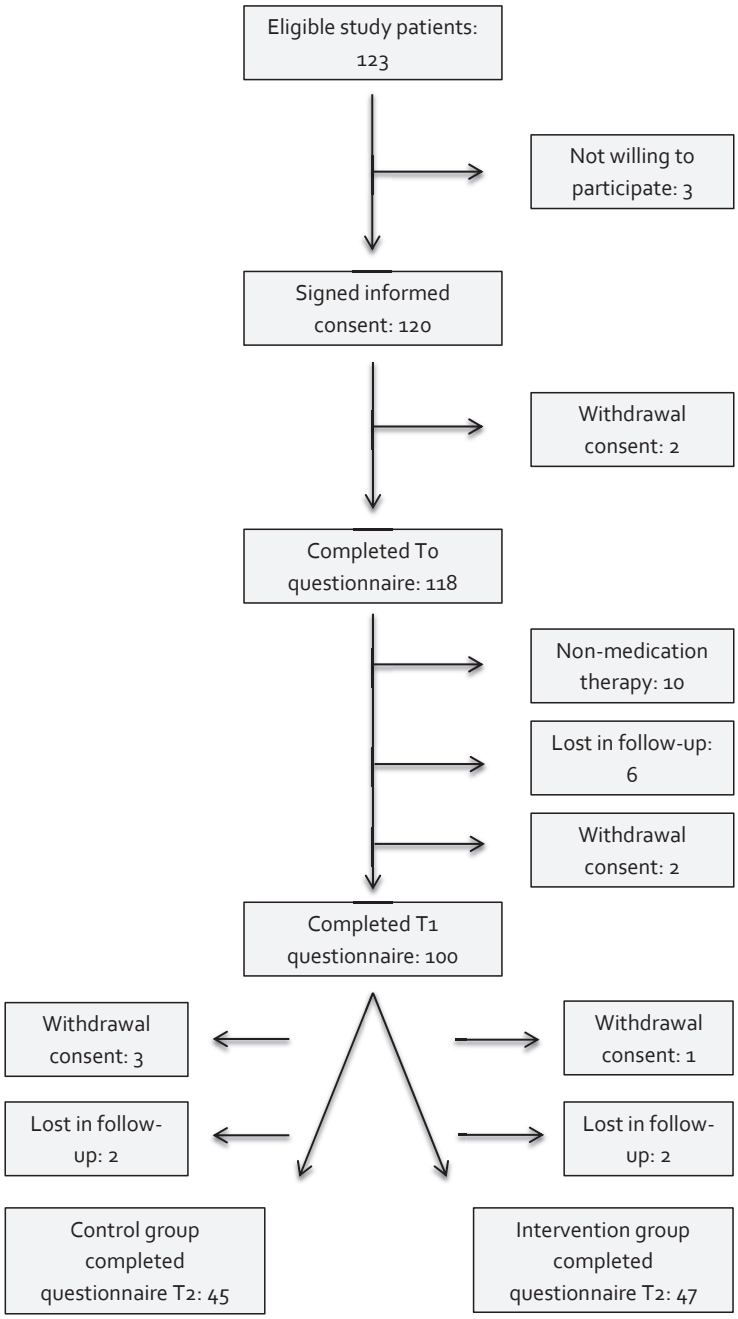

Figure 1. Study Flowchart

Demographics

Demographic variables of the included patients, i.e., level of education, diagnoses and number of other medications, are presented in Table 1. There were no significant differences between the control group and intervention group. Baseline characteristics in patients that did not finish the study did not differ from patients that did finish the study. Medications prescribed at T0 and T1 are presented in Table 2.

Table 1. Demographics

		Control (n=45)	Intervention (n=47)	
Age (SD)		60.2 (14.0)	58.5 (12.7)	p=0.52
Gender (n(%))	male	17 (38)	24(51)	
	female	28 (62)	23(49)	p=0.20
Mean Pain intensity	mean (SD)	7.4 (1.4)	7.3 (1.6)	p=0.84
Maximum Pain intensity	mean (SD)	8.5 (1.0)	8.3 (1.3)	p=0.40
Level of education (n(%))	Level 1. Primary education	1 (2)	4 (8)	
	Level 2. Lower secondary education	9 (20)	10 (21)	
	Level 3. Upper secondary education	9 (20)	13 (28)	
	Level 4. Post-secondary non-tertiary education	18 (40)	14 (30)	
	Level 5-6. Tertiary education	8 (18)	6 (13)	p=0.28
Diagnosis (n(%))	Low back pain	11(25)	17 (37)	
	Neuropathic pain	17 (39)	16 (34)	
	Spinal canal stenosis	2 (4)	4 (9)	
	Neck pain	1 (2)	2 (4)	
	Arthritis	1 (2)	2 (4)	
	Atypical thoracic pain	0 (0)	1 (2)	
	CRPS type 1	1 (2)	0 (0)	
	Failed back surgery syndrome	5 (11)	2 (4)	
	Fibromyalgia	3 (7)	2 (4)	
	Frozen shoulder	2 (4)	0 (0)	
	Ischemic pain	1 (2)	1 (2)	
	Whiplash associated disorder	1 (2)	0 (0)	p=0.61

Medication Adherence

The rates of non-adherence are presented in Table 3. The study allocation did not contribute to the prediction of non-adherence. Of the patients who reported underuse at T1, 39% of them did so intentionally; the others simply forgot to take their medication. At T2, 38% of the self-reported under-users did so intentionally. All patients that admitted medication overuse were intentional over-users.

Table 2. Prescribed medication during visits at T0 and T1. IR=immediate release; LA=long-acting; CR=continued release.

		T0		T1	
		Control n (%)	Intervention n(%)	Control n(%)	Intervention n(%)
Non-opioids					
	NSAIDs	3 (7)	4 (8)	5 (11)	3 (6)
	Anti-convulsants	14 (31)	14 (30)	13 (29)	14 (30)
	Anti-depressants	5 (11)	7 (15)	6 (13)	6 (13)
	Anti-convulsants & anti-depressants	5 (11)	3 (6)	4 (9)	4 (9)
Opioids					
	IR-opioids (tramadol, codeine)	5 (11)	5 (11)	3 (7)	2 (4)
	LA-/ CR-opioids (oxycontin, fentanyl)	11 (25)	10 (22)	9 (20)	12 (25)
Opioids and non-opioids					
	LA-/ CR-opioids & anticonvulsants	0	4 (8)	3 (7)	4 (9)
	LA-/ CR-opioids & antidepressants	1 (2)	0	0	1 (2)
	IR-opioids & anticonvulsants	1 (2)	0	2 (4)	1 (2)
Total		45 (100)	47 (100)	45 (100)	47 (100)

Table 3. General non-adherence, underuse and overuse at T1 and T2.

		Control	Intervention	Binary logistic regression
Non-adherence n(%)	T1	14/45 (31)	20/47 (43)	
	T2	24/45 (53)	23/47 (49)	p=0.42
Underuse n(%)	T1	11/45 (24)	15/47 (32)	
	T2	19/45 (42)	20/47 (43)	p=0.75
Overuse n(%)	T1	5/45 (11)	7/47 (15)	
	T2	7/45 (16)	8/47 (17)	p=0.96

The rates of non-adherence, underuse and overuse did not differ significantly between non-opioid users and opioid users in a secondary analysis at T2 (Table 4) . Furthermore, patterns of non-adherence did not differ significantly between direct-acting pain medication and slow-onset neuropathic pain medication (anti-convulsants and anti-depressants).

Knowledge

Knowledge scores at T1 and T2 are presented in Table 5. No significant effect of Group was found. Overall the knowledge between T1 and T2 improved significantly (Time), ($p < 0.01$). In addition, in the intervention group the knowledge of the prescription was significantly improved compared to the control group (Time*Group), ($p <= 0.01$).

Table 4 . Type of medication and frequency of non-adherence at T2.

	Opioids	Non-opioids	p
Non-adherence n (%)	18 (47)	29 (54)	0.67
Underuse n (%)	12 (32)	27 (50)	0.09
Overuse n (%)	9 (24)	6 (11)	0.15
	Anti-convulsants & anti-depressants	**Direct-acting pain medication**	
Non-adherence n (%)	27 (51)	20 (51)	1.0
Underuse n (%)	25 (47)	14 (36)	0.30
Overuse n (%)	6 (24)	9 (23)	0.16

Table 5. Results of the MANOVA analyses on knowledge and treatment outcome parameters. * $p < 0.05$; ** $p < 0.01$.

Outcome parameter		Control mean (SD)	Intervention mean (SD)	Time	Group	Time * Group
Knowledge (0-4)	T1 T2	3.1 (1.3) 3.1 (0.9)	2.6 (1.2) 3.3 (1.0)	$F_{(1,89)}=7.0^{**}$	$F_{(1,89)}=0.61$	$F_{(1,89)}=7.0^{**}$
Mean pain intensity (NRS)	T1 T2	6.3 (1.9) 6.1 (1.8)	6.3 (2.0) 5.4 (2.2)	$F_{(1,90)}=7.26^{**}$	$F_{(1,90)}=1.11$	$F_{(1,90)=}3.29$
Maximum pain intensity (NRS)	T1 T2	7.5 (1.8) 7.5 (1.5)	7.2 (2.0) 6.5 (2.4)	$F_{(1,90)}=1.9$	$F_{(1,90)}=4.1^{*}$	$F_{(1,90)}=2.50$
Perceived improvement (0-5)	T1 T2	3.5 (1.1) 3.6 (0.9)	3.6 (0.9) 3.7 (0.9)	$F_{(1,90)}=0.53$	$F_{(1,90)}=0.41$	$F_{(1,90)}=0.03$
Patient satisfaction (0-5)	T1 T2	3.8 (1.4) 4.3 (1.4)	4.0 (1.2) 4.3 (1.3)	$F_{(1,90)}=4.6^{*}$	$F_{(1,90)}=0.23$	$F_{(1,90)}=0.51$

Treatment outcome

Treatment outcome measurements are presented in Table 5. There was no significant Group effect on mean pain intensity, but mean pain intensity in both study groups improved between T1 an T2 (Time; p=0.008; table 3). However, there were no significant differences in mean pain intensities attributable to treatment allocation (Time*Group; p=0.07). From T1 to T2, maximum pain intensities were significantly higher in the control group (Group; p<0.05). Time effect on maximum pain intensity was not significant. Differences were not attributable to allocation (Time*Group; p=0.12). Overall, the mean and maximum pain intensity between T0 and T2 improved (Time; p<0.001 and p< 0.001, respectively; data not shown).

Group effect was not significant for patient satisfaction. Whereas Time factor resulted in improved satisfaction in both groups (p<0.05), Time*Group interaction was not significant.

Concerns towards pain medication

Mean scores on the seven subscales of the PMAQ are presented in Table 6. Complete data were available for 42 patients in the control group and 39 patients in the intervention group. The factor Group, neither Time nor Time * Group yielded a significant effect.

Table 6. Concerns about medication according to the PMAQ (0=never true to 5=always true) and results of the MANOVA analysis. No significant differences were found.

Concerns		Control mean (SD)	Intervention mean (SD)	Time	Group	Time * Group
Addiction	T1	2.0 (1.1)	1.9 (1.0)	$F_{(1,79)}$=0.001	$F_{(1,79)}$=1.5	$F_{(1,79)}$=3.0
	T2	2.2 (1.3)	1.7 (0.7)			
Percieved need	T1	3.4 (0.6)	3.3 (0.6)	$F_{(1,79)}$=3.0	$F_{(1,79)}$=0.22	$F_{(1,79)}$=0.005
	T2	3.3 (0.8)	3.2 (0.7)			
Scrutiny	T1	1.5 (0.6)	1.5 (0.6)	$F_{(1,79)}$=0.76	$F_{(1,79)}$=0	$F_{(1,79)}$=0.021
	T2	1.6 (0.6)	1.5 (0.7)			
Side effects	T1	2.6 (1.1)	2.5 (0.9)	$F_{(1,79)}$=1.5	$F_{(1,79)}$=0.58	$F_{(1,79)}$=0.58
	T2	2.9 (1.2)	2.6 (1.0)			
Tolerance	T1	2.6 (0.9)	2.6 (0.8)	$F_{(1,79)}$=0.17	$F_{(1,79)}$=0.9	$F_{(1,79)}$=1.6
	T2	2.8 (0.9)	2.5 (0.8)			
Mistrust	T1	1.7 (0.7)	1.9 (0.8)	$F_{(1,79)}$=0.21	$F_{(1,79)}$=0.54	$F_{(1,79)}$=3.4
	T2	1.8 (0.6)	1.7 (0.8)			
Withdrawal	T1	2.3 (1.1)	2.2 (0.8)	$F_{(1,79)}$=3.9	$F_{(1,79)}$=0.01	$F_{(1,79)}$= 1.3
	T2	2.4 (1.5)	2.4 (0.9)			

DISCUSSION AND CONCLUSION

Discussion

An educational intervention by means of a DVD presentation combined with written information about the prescribed medication did not result in improved medication adherence compared to standard care in pain patients treated with new pain medication. It did, however, result in better knowledge of the prescribed therapy compared to the control group. Although a favorable trend towards an effect on mean pain intensity was found, treatment outcome variables and attitudes towards pain medication were not significantly altered by standardized medication-specific education compared to standard care.

Although knowledge has been associated with adherence, health belief models provide an explanation for the non-significant results of the study. As demonstrated by the information-motivation-behavioral skills (IMB) model of Fisher and Fisher, information is a prerequisite for changing non-adherence behavior, but in itself insufficient to create this change.[10] Motivation and behavioral skills are critical determinants and are independent predictors of behavior change as well (Figure 2). Low motivation decreases the likelihood of adherence, even in a highly informed patient. A single educational intervention may not be able to improve motivation or behavioral skills, and for this reason it fails to produce significant changes in adherence behavior in this study.

In order to be effective in improving medication adherence, some important aspects of the educational program might be restructured. First, the contents of the videos themselves should be reconsidered. Instead of limiting the information to details about prescribed medication, education outcomes might improve by providing additional information about chronic pain as

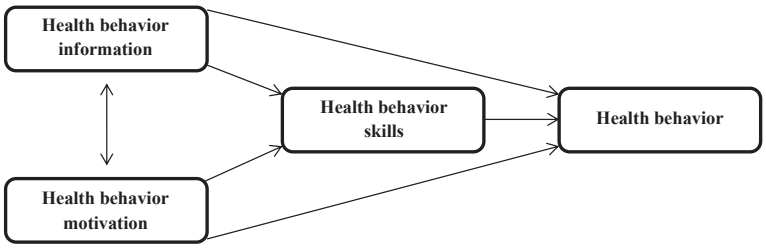

Figure 2. Information-motivation-behavioural skills (IMB) model. Note. Reprinted from Fisher, W. A., Fisher, J. D. and Harman, J. (2003) The Information-Motivation-Behavioral Skills Model: A General Social Psychological Approach to Understanding and Promoting Health Behavior, in Social Psychological Foundations of Health and Illness (eds J. Suls and K. A. Wallston), Blackwell Publishing Ltd, Malden, MA. Copyright 2009 Wiley-Blackwell. Reprinted with permission.

a disease, including treatment options, thereby placing prescribed medication into the context of a structured treatment approach. Furthermore, emphasizing the importance of medication adherence and providing practical tools to prevent non-intentional adherence may further improve the effect of the video on medication adherence. Secondly, the information provided might be more effective when it is offered in a *patient-tailored* manner by addressing individual needs and concerns of patients and their prejudices about pain medication.[11-15] This could be achieved by tailored discussions with health care providers. Thirdly, *repeated* educational counselling including assessment of adherence behavior, ideally embedded in routine care, is probably more effective that a single educational intervention.[12,13] Alternatively, this could be achieved by planned telephone coaching, patient-tailored eHealth or mHealth applications.[14-16] Finally, education should ideally be part of a larger self-management program containing behavioral and motivational support to create lasting behavioral changes and improvement of self-efficacy. However, these programs are complex and labor-intensive, making it difficult to see how they could be carried out in a non-research setting.[17] Tailored internet-based support has shown promising results and might be a realistic way to provide long-term monitoring capabilities and patient support.[18]

As described in most studies, medication adherence was, again, disappointing.[3] At the end of the study, half of the patients were non-adherent, regardless of their study allocation. Underuse was more common than overuse in both opioid and non-opioid users, as was described in earlier studies.[11,19] The type of medication did not predict the direction of non-adherence. Although a trend towards less underuse in opioid users compared to non-opioid users at T2 was found, differences were not significant. To increase the reliability of the results, we used a combination of two self-report measures to assess adherence.[20] Simply asking patients whether they used their medication or not resulted in higher adherence scores than use of the Morisky adherence scale. Nevertheless, the scores of both measurements had a common variance of .25 ($p<0.001$).

In our previous study, we found a positive association between knowledge and medication adherence.[6] We did not find this in the current study in a post hoc bivariate analysis (Pearson

correlation coefficient (T2) -0.117; p=0.27). This may be explained by methodological differences between both studies. Medication adherence was defined differently in this study, and instead of asking one question about medication use on the previous day we assessed adherence in a longer time frame using a combination of methods. Furthermore, the previous study was performed in a University hospital. Our second study took place in a large general hospital. Standard care and the patient population might have been different.

During this study, there was a significant reduction of mean and maximum pain intensities, which might be caused by the newly prescribed medication. The overall improvement of pain intensities, however, was modest. We did not find a correlation between medication adherence and mean pain intensity improvement or patient satisfaction (post-hoc bivariate correlation analysis, correlation coefficient (T2) -0.009; p=0.931 and 0.157; p=0.136, respectively). Although some studies describe an association, a causal relationship between medication adherence and treatment outcome has never been demonstrated in chronic pain.[21] Chronic pain is a complex disease, and therapy outcome is determined by multiple factors as diagnosis, psychological and socio-economic factors. The effect of medication is often limited, thereby automatically limiting the negative effect of non-adherence to this therapy on pain treatment outcome. Besides, patients may be satisfied with less than perfect analgesia and may prioritize other outcomes.[22] Patients may think they are doing the right thing when they don't take their medications, especially if symptoms are acceptable. It may be reasonable to study the relationship between medication adherence and treatment outcome in chronic pain before investigating further interventions focused on improving medication adherence.

A limitation of this study might be the high number of patients who did not complete one or more questionnaires. Reasons were that they either were lost in follow-up, refused to repeatedly answer questionnaires or that a different treatment without pain medication was initiated during the study. Although no significant demographical differences were found between patients that did or did not finish the study, non-adherence levels may be different in patients who do not keep hospital appointments or study agreements. Another limitation is the use of self-report measurements of adherence instead of more objective methods as urine analysis or electronic pill bottles. Although self-report is more easily used in clinical studies and daily practice, it is susceptible to overestimation of adherence. A final important consideration in this study is that medication adherence, although presented as a dichotomous variable, is actually a complex behavioral pattern. It ranges from complete non-compliance to strict adherence to prescribed therapy, and it is dynamic and can change from day to day.

Do we have to provide medication-specific information on video to our patients? Patients should receive adequate information to make the best decisions for themselves about their own health and healthcare. An educational video may increase basic knowledge of the prescription, and it can be used as an additional and inexpensive tool to explain the described therapy to pain patients and answer frequently asked questions. Nevertheless, it might not largely affect outcome.

Conclusion

In conclusion, a medication specific educational intervention did not result in better medication adherence or improved treatment outcome compared to standard care, nor did it significantly alter patients concerns about medication. It did improve knowledge of the prescribed therapy. Moreover, there was no association between medication adherence and treatment outcome. Future studies should focus on the effects and cost-effectiveness of patient-tailored adherence interventions, motivational interviewing and behavioral support on pain medication use. More importantly, they should investigate the importance of strict medication adherence on pain therapy outcome.

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CHAPTER 5

Comparison of the effect of intensified hospital-initiated follow-up, patient-initiated follow-up and standard care on medication adherence in patients with chronic pain: a randomized controlled clinical trial.

Leon Timmerman
Dirk L. Stronks
George Groeneweg
Frank J.P.M. Huygen

Submitted

ABSTRACT

Introduction

Non-adherence to pain medication is common and may lead to poorer treatment outcomes. It is unknown which follow-up strategies could optimize medication adherence and pain treatment effects.

Aim

The objective of this randomized controlled clinical study was to compare the effect of three different follow-up strategies on medication adherence, therapy outcome and health care consumption in chronic non-malignant pain patients.

Methods

Three follow-up strategies were compared: (1) standard care, (2) intensive hospital-initiated follow up, in which patients were contacted every two weeks, and (3) intensive patient-initiated follow-up, in which patients received standard care and additional follow-up on their demand. Primary outcome measure was medication adherence. Secondary outcome measures were pain intensity, patients satisfaction and number of patient contacts.

Results

The level of medication adherence did not differ between the three offered follow-up strategies. Furthermore, changes in pain intensities, patient satisfaction regarding medication, the care provided or the effect of pain treatment did not differ between the follow-up strategies. Compared to standard care, patient satisfaction regarding the provision of information was higher in the two other groups. The number of unplanned patient contacts did not differ between the study groups.

Conclusion

There was no difference in medication adherence between standard follow-up, intensified hospital-initiated follow-up or patient initiated follow-up in chronic pain patients. Except for the satisfaction regarding the information provided, treatment outcomes did not differ between these follow-up strategies as well. Patient initiated follow-up might be an acceptable and cost-effective alternative for long-term follow-up of chronic non-malignant pain patients.

INTRODUCTION

Chronic pain has been reported by about one in five adults throughout the world.[1] Pharmacotherapy is an important component of pain therapy. Pain-relievers top the list of therapeutic drugs prescribed during visits to physician offices and emergency rooms.[2] It is well recognized that pain perception as well as pain relief after analgesic therapy display large interindividual variability.[3] Age, gender, ethnicity and actual level of stress, mood or diseases may modify individual pain perception and responses to drug treatment.[3] Furthermore, pharmacogenetic differences may lead to pharmacokinetic and –dynamic differences.[4] Any of these factors may play a role in the (sub-optimal) effect of an analgesic treatment.

Another important reason for sub-optimal treatment response might be that up to 40% of chronic pain patients do not use their medication as prescribed.[5] Although the consequences of poor medication adherence in chronic pain patients are less clear than in other chronic conditions, it seems plausible that it leads to a reduced clinical benefit, increased burden of side effects, medication wastage and increased healthcare costs as well.[6] Furthermore, when physicians are unaware of patients' non-adherence to their prescribed medications, treatment effect could be misinterpreted leading to unnecessary therapy changes.

Factors that have been found to be negatively associated with pain medication adherence are younger age, polypharmacy, poor quality of the doctor-patient relationship, concerns towards pain medication and little knowledge of medication prescribed.[5,7] Until now, knowledge of these factors has not been used to develop effective interventions to improve pain medication adherence. In other chronic conditions, successful interventions aimed at enhancing medication adherence have been reported and shown to be complex, and mostly consisted of frequent patient tailored counselling and education, and ongoing support from health care professionals.[8]

In chronic pain management, it is unknown which follow-up strategy is effective in fostering adequate medication adherence. Although traditional patterns of patient follow-up vary, most patients initially visit their physician every six to twelve weeks, until the course of the condition has been established. A more intensive, hospital-initiated, follow-up strategy with more frequent evaluations of the effect of prescribed medication, tailored discussion of concerns, and ongoing reassurance might improve medication adherence and therapy outcome.[8] However, this could well lead to overbooked outpatients services on the one hand, and increased number of unnecessary visits on the other.

Patient initiated follow-up is another upcoming model of care which has been investigated in other chronic conditions as inflammatory bowel disease, rheumatology and breast cancer. The aim of patient-initiated follow-up is to be responsive to the patient need.[9-11] The patient decides if and when to consult a specialist, which may reduce unnecessary appointments. Patient-initiated follow-up might lead to a shift of medical utilities to patients who actually need these facilities. Furthermore, if the patient is empowered to initiate a specialist review, feelings of enhanced

self-efficacy and control may grow and consequently lead to improvement of clinical and psychological outcome. Up to now, patient-initiated care studies have shown promising results regarding patient satisfaction and health care efficiency. When combined with low-frequent planned consultation, the risk of harm is reported to be low.[9-11] However, routine monitoring of medication adherence is difficult when medical care is delivered on demand. Therefore, the effect of patient-initiated follow-up on medication adherence is difficult to determine.

The objective of this randomized controlled clinical study was to compare the effect of three different follow-up strategies on medication adherence, therapy outcome and health care consumption, after a new prescription of analgesics in chronic non-malignant pain patients.

METHODS

After approval by the medical ethics committee, this randomized controlled clinical trial was performed at the pain treatment center of a large general hospital in the Netherlands. Patients at this treatment center are commonly referred by general practitioners, neurologists, neurosurgeons, orthopaedic surgeons or plastic surgeons. All patients with non-malignant pain existing longer than 3 months who received a new analgesic prescription or who received additional pain medication to an existing treatment regimen, were invited to participate. Participants had to be able to complete electronic questionnaires in the Dutch language. Patients receiving medication on an 'as needed' basis and patients younger than 18 years were excluded. All participants provided written informed consent.

Procedures

All eligible patients received information about this study. As a part of standard care, a follow-up visit after 6 weeks was planned. After receipt of informed consent an email was sent containing a link to the web-based baseline questionnaire. After two weeks and after eleven weeks, the first and second follow-up questionnaires were sent. These follow-up questionnaires were identical.

After receipt of the first follow-up questionnaire, patients were randomized to one of the three study groups: (1) standard follow-up, which consisted of follow-up visits after 6 and 12 weeks; (2) intensified hospital-initiated follow-up, which consisted of standard follow-up and additional scheduled counselling by a specialized nurse after 3, 5, 8 and 10 weeks; or (3) patient-initiated follow-up, which consisted of standard follow-up and additional counselling at patients' request. Patients in the patient-initiated follow-up group were contacted by a specialized nurse as soon as possible, at least within 48 hours upon request for additional evaluation. For allocation of the participants, a computer-generated list of random numbers was used with a single block of 120 patients and 1:1:1 allocation ratio. Independent nurses of the pain treatment center allocated participants to one of the three study arms, and arranged additional contacts if needed according to the study allocation.

Outcome measures

Baseline data collected were: age, sex, level of education, mean and maximal pain intensity in the past week (using an 11-point numeric rating scale (NRS)), duration of symptoms and number of different medications.

Primary outcome measure was medication adherence measured 2 and 11 weeks after initiation of a new prescription. Adherence was measured by asking two questions. One question measured underuse of pain medication: 'You received a prescription for pain medication from your doctor. How often do you, intentionally or unintentionally, miss or skip a dose? '. The second question measured overuse of pain medication: 'How often do you take more medication than prescribed? Answers were given on a 6 point scale (0=never, 1=seldom, 2= once a month, 3=once a week, 4 more than once a week, not every day, 5=every day).

Mean and maximal pain intensity in the previous week (NRS) were registered as secondary outcome measures at baseline, and after 2 and 11 weeks. After 2 and 11 weeks, satisfaction with treatment of pain was assessed using the Dutch translation of the Pain Treatment Satisfaction Scale (PTSS), generously provided by MAPI Research Trust, Lyon, France. The PTSS is a valid comprehensive instrument, consisting of seven independent modules and seven stand-alone questions, that has demonstrated satisfactory psychometric quality.[12] The following items were used:

(1) module '*satisfaction with information about pain and its treatment*' (5 questions, e.g. how much information would you have liked to have about your illness or injury?)
(2) module '*satisfaction with medical care*' (5 statements, e.g. it is easy to ask the medical staff questions)
(3) module '*Satisfaction with the effects of current pain medication*' (8 statements, e.g. my pain medication helps me have a better outlook on life)
(4) module '*side effects of medication*' (identification of side effects)
(5) module '*satisfaction with current medication and care*' (9 statements, e.g. are you satisfied about the amount of time the doctors devoted to you during the visits? Are you satisfied about the amount of medication you take?)
(6) overall patient satisfaction (3 stand-alone questions, e.g. would you like to continue your current pain medication?).

Furthermore, the names of the medications used were registered after 2 and 11 weeks. Following the final study visit after 12 weeks, the numbers of planned and unplanned contacts were registered.

Data analysis

Underuse was defined as missing a dose every week up to every day. Overuse was defined as taking additional medication every week up to every day. Non-adherence was defined as underuse and/or overuse of pain medication.

The subscales of the PTSS were scored as follows: *Satisfaction with information about pain and its treatment*: mean score of five items (individual scores ranging from 1 (I would have

liked much more information), 3 (the information was right for me) to 5 (I would have liked no information)) were categorized into 3 groups (0<3 = would have preferred more information; 3 = right amount of information; >3 = would have preferred less information); *Satisfaction with medical care*: mean score of five items, ranging from 1 (very positive) to 5 (very negative). *Satisfaction with the effects of current pain medication*: mean score of eight items, ranging from 1 (very positive) to 5 (very negative). *Satisfaction with current medication and care* mean score of nine items, ranging from 1 (very satisfied) to 5 (very dissatisfied). The remaining questions were stand-alone questions analysed as such, all scored a 1 (very positive) to 5 (very negative).

Statistical analysis

Regarding the absence of previous comparable studies, we chose to use a statistical detectable and clinically relevant within/between interaction effect size (f(V)) of 0,3 on medication adherence, with a power (1-β) of 0,8, allocation ratio of 1:1:1 and a two-sided significance level of 0.05. The a priori sample size requires 37 patients per study arm. To correct for possible data loss, we planned to include 120 patients into the study.

Descriptive statistics were used to determine the frequencies of the demographic variables and the outcome parameters and to describe measures of central tendency and dispersion dependent on the shape of their distribution. The shape of the distribution was analysed by using the Kolmogorov-Smirnov test. Differences in proportions between the experimental groups at baseline were tested using the Pearson Chi square Test. Differences in continuous variables were evaluated using the Independent- Samples Kruskal-Wallis Test if the parameter was not normally distributed and the One Way ANOVA if the parameter was normally distributed.

Binary logistic regression analysis was used to evaluate the contribution of the follow-up strategy to the prediction of adherence to the prescribed medication at 11 weeks using experimental group and adherence at 2 weeks as a covariate.

Differences in pain intensities, PTSS-items and number of contacts between experimental groups over time (week 2 to 11) were analysed by means of MANOVA for repeated measures. Experimental group and time were the independent variables.

For the non-normal distributed variables we still decided to use multivariate analysis of variance (MANOVA)test. Although MANOVA test requires that each dependent variable entered into the analysis be normally distributed it was still used because the Monte Carlo experiments have shown that for sample sizes of 3 or 5 it is still possible to analyse leptokurtic, rectangular, J-shaped, moderately, and markedly skewed distributions. These experiments demonstrated that the empirically determined rejection region of the F-distribution would be no larger than $\alpha = 0.08$ when the usual 5% rejection is used.[13] The results are therefore presented as mean ± standard deviation (SD).

For all statistics, alpha was set at the traditional 0.05 level. All analyses were performed using IBM SPSS Statistics version 24 (SPSS, Inc, Chicago, IL).

RESULTS

From November 2014 up to November 2016, 152 patients consented to participate. One hundred-and-thirty-three patients responded to the baseline questionnaire. One-hundred-and-twenty patients responded to the first follow-up questionnaire after two weeks and were randomized. Finally, one hundred and two patients responded to the final questionnaire after 11 weeks.

Demographics

Demographic data are presented in table 1. The pain diagnoses generally included patients with radiculopathy, peripheral neuropathy, polyneuropathy and low back pain (supplemental table S1). The different medications prescribed included NSAIDS, opioids, anticonvulsants and antidepressants (supplemental table S2).

Table 1. Demographics

		Standard care (N=40)	Intensive follow-up (N=40)	Patient Initiated follow-up (N=40)	
Age (mean (SD))		59.7 (12,6)	54.3 (13,6)	55.7 (12,9)	p=0.17
Gender (n (%))	Male	15 (37)	13 (33)	18 (45)	p=0.51
	Female	25 (63)	27 (67)	22 (55)	
Level of education (n(%))	Primary education	0 (0)	2 (5)	1 (2)	p=0.99
	Lower secondary education	11 (28)	10 (25)	11 (27)	
	Upper secondary education	9 (22)	7 (17)	7 (18)	
	Post-secondary non-tertiary education	12 (30)	13 (33)	15 (38)	
	Tertiary education	8 (20)	8 (20)	6 (15)	
Mean Pain intensity (NRS) baseline	mean (SD)	6.3 (1,7)	6.1 (1,7)	6.3 (1.8)	p=0.85
Max Pain intensity (NRS) baseline	mean (SD)	7.8 (1.4)	7.6 (1.3)	7.8 (1.4)	p=0.90
Number of different medications (n (%))	1	4 (10)	6 (15)	5 (13)	p=0.13
	2	4 (10)	4 (10)	0 (0)	
	3	3 (8)	8 (20)	2 (5)	
	4	5 (12)	5 (13)	9 (23)	
	5 or more	24 (60)	17 (42)	24 (59)	
Pain duration (n(%))	0-3 months	0 (0)	0 (0)	0 (0)	p=0.95
	3-6 months	1 (2)	5 (13)	4 (10)	
	6-12 months	6 (15)	4 (10)	8 (20)	
	1-2 years	10 (25)	8 (20)	3 (8)	
	2-3 years	10 (25)	6 (15)	4 (10)	
	3-5 years	1 (3)	5 (12)	8 (20)	
	more than 5 years	12 (30)	12 (30)	13 (32)	

Medication non-adherence

There were no differences in the rates of non-adherence (p=0.19), underuse (p=0.86) or overuse (p=0.06) between the three experimental groups. Details on medication non-adherence are presented in table 2.

Table 2. Nonadherence to pain medication in the study groups by moment of measurement.

			11 weeks non-adherence		
			yes	No	Total
Standard Care	2 weeks non-adherence	yes	5 (14%)	4 (11%)	9 (25%)
		no	2 (6%)	25 (69%)	27 (75%)
		Total	7 (19%)	29 (81%)	36 (100%)
Intensive hospital-initiated follow-up	2 weeks non-adherence	yes	0 (0%)	3 (9%)	3 (9%)
		no	3 (9%)	28 (82%)	31 (91%)
		Total	3 (9%)	31 (91%)	34 (100%)
Intensive patient-initiated follow-up	2 weeks non-adherence	yes	5 (17%)	2 (7%)	7 (24%)
		no	4 (14%)	18 (62%)	22 (76%)
		Total	9 (31%)	20 (69%)	29 (100%)
			11 weeks underuse		
			yes	No	Total
Standard Care	2 weeks underuse	yes	3 (8%)	3 (8%)	6 (17%)
		no	2 (6%)	28 (78%)	30 (83%)
		Total	5 (14%)	31 (86%)	36 (100%)
Intensive hospital-initiated follow-up	2 weeks underuse	yes	0 (0%)	2 (6%)	2 (6%)
		no	3 (9%)	29 (85%)	32 (94%)
		Total	3 (9%)	31 (91%)	34 (100%)
Intensive patient-initiated follow-up	2 weeks underuse	yes	3 (10%)	2 (7%)	5 (17%)
		no	2 (7%)	22 (76%)	24 (83%)
		Total	5 (17%)	24 (83%)	29 (100%)
			11 weeks overuse		
			yes	No	Total
Standard Care	2 weeks overuse	yes	2 (6%)	1 (3%)	3 (8%)
		no	1 (3%)	32 (89%)	33 (92%)
		Total	3 (8%)	33 (92%)	36 (100%)
Intensive hospital-initiated follow-up	2 weeks overuse	yes		1 (3%)	1 (3%)
		no		33 (97%)	33 (97%)
		Total		34 (100%)	34 (100%)
Intensive patient-initiated follow-up	2 weeks overuse	yes	3 (10%)	0 (0%)	3 (10%)
		no	2 (7%)	24 (83%)	26 (90%)
		Total	5 (17%)	24 (83%)	29 (100%)

Across all study participants, general non-adherence rate before randomization after 2 weeks was 22%, underuse rate was 16% and overuse rate was 8%. Post-randomization non-adherence rate after 11 weeks was 19%, underuse rate was 13% and overuse rate was 8%. Overuse occurred significantly more in opioid users (supplemental table S3). There was no difference in patterns of non-adherence in patients taking direct acting pain medications (NSAIDs, opioids, other pain medications) compared with patients taking anticonvulsants or antidepressants.

Pain intensity

Mean pain intensities at baseline, 2 weeks and 11 weeks in the study groups are shown in figure 1. There was no significant group effect (p=0.46). Time effect was small but significant (p=0.017) and consisted of an increase in mean pain intensity after 2 weeks followed by a decrease after 11 weeks. Study allocation did not contribute to changes observed over time (Time*Group; p=0.98).

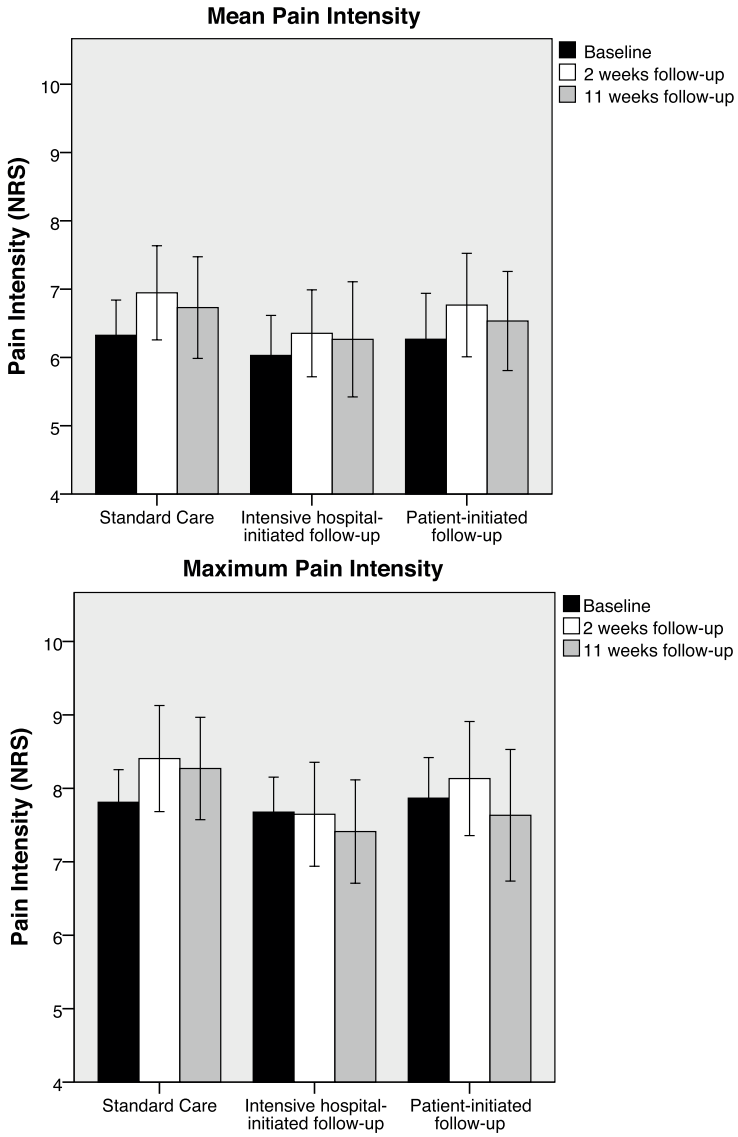

Figure 1. Pain intensities (mean(SD)) in the study groups by moment of measurement.

Maximum pain intensities are shown in figure 1. Factor time (p=0.28), group (p=0.27) and time*group were not significant. There was no significant difference between the groups (p=0.27), nor over time (p=0.28). Likewise, there was no significant interaction between the groups and time (p=0.51).

Pain treatment satisfaction

Results of the PTSS module 'Satisfaction with information about pain and its treatment' are presented in table 3. There was no significant effect of Time (p=0.13) or Group (p=0.54), but treatment allocation contributed significantly to the changes between week 2 and week 11 (Time*Group; p=0.02). Results of the PTSS modules 'Satisfaction with medical care', 'Satisfaction with the effect of current pain medication' and 'Satisfaction with current medication and care received' are outlined in figure 2. No significant Time, Group, or Time*Group effects were observed in these modules. Stand-alone PTSS questions regarding the general satisfaction about current pain medication, concordance between experienced and expected pain relief and the wish to continue current pain medication are outlined in figure 3. There were no significant differences found in the analyses of these items as well. A majority of patients suffered some side effects up to unacceptable side-effects. The reports of side effects at T2 are documented in table 4.

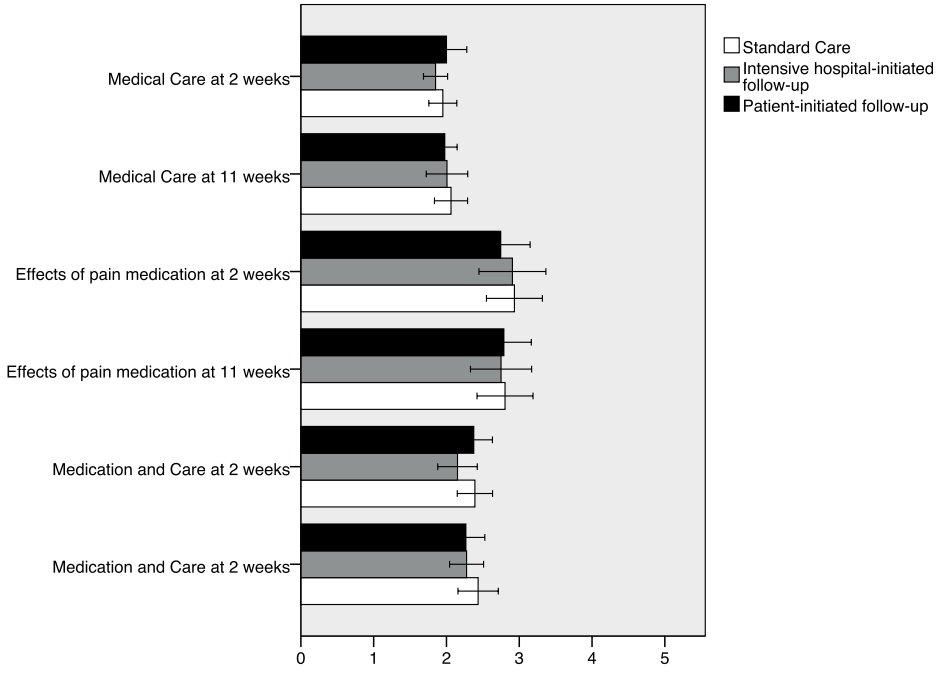

Figure 2. Results of the PTSS modules 'Satisfaction with medical care', 'Satisfaction with the effect of current pain medication' and 'Satisfaction with current medication and care received'(mean(SD)). Scores range from 1 (very satisfied) to 5 (very dissatisfied).

Table 3. Results of PTSS module 'Satisfaction with information about pain and its treatment'.

	Information	Standard care	Intensive follow-up	Patient Initiated follow-up	Time*Group
	Preferred more	26 (70%)	26 (68%)	31 (82%)	
Week 2	Enough	10 (27%)	11 (29%)	7 (18%)	
	Preferred less	1 (3%)	1 (3%)	0	$F_{(2,89)} = 4.1$; p=0.020
	Preferred more	26 (74%)	19 (58%)	16 (57%)	
Week 11	Enough	9 (26%)	14 (42%)	9 (32%)	
	Preferred less	0	0	3 (12%)	

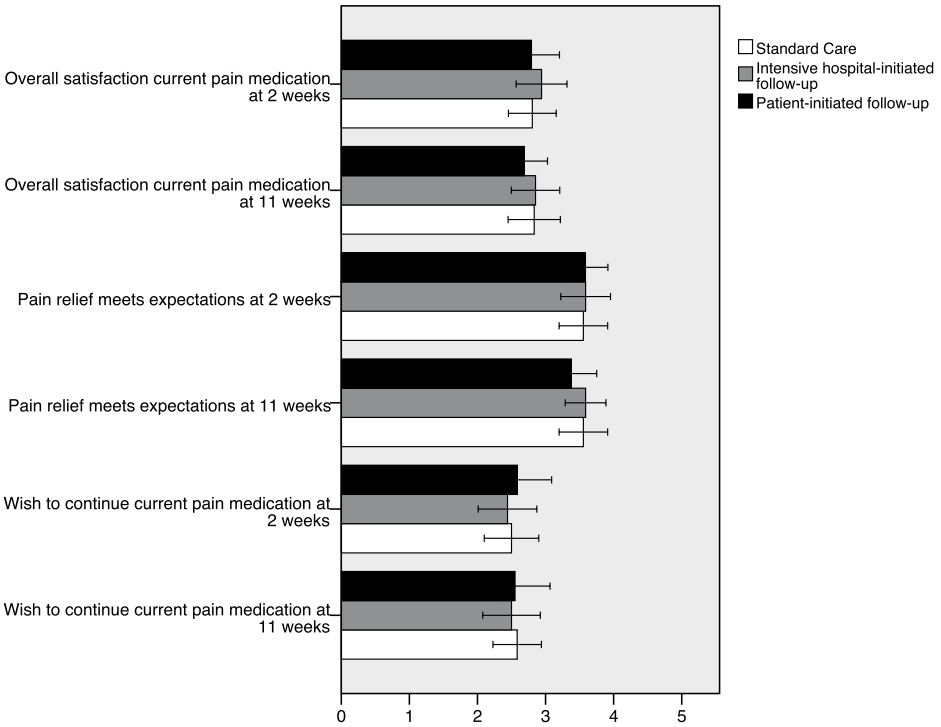

Figure 3. Results of the PTSS stand-alone questions (mean(SD)). Scores range from 1 (very positive) to 5 (very negative).

Number of contacts

Mean number of planned contacts were 2.9 (0.6), 5.4 (1.4) and 2.8 (0.6) in group S, INT and PI, respectively. Mean number of unplanned contacts were 0.5 (0.8), 0.3 (0.6) and 0.7 (2,0) in group S, INT and PI, respectively (p=0.38).

Table 4. Side effects of pain medication.

	Side effects	Standard care	Intensive follow-up	Patient Initiated follow-up	Time*Group
2 weeks follow-up	none	10 (25%)	4 (10%)	9 (24%)	$F_{(2,96)}$=0.47; p=0.62
	little	11 (27%)	8 (20%)	8 (21%)	
	some	13 (32%)	17 (42%)	13 (34%)	
	many	5 (13%)	8 (20%)	6 (16%)	
	unacceptable	1 (3%)	3 (8%)	2 (5%)	
11 weeks follow-up	none	15 (42%)	5 (15%)	8 (28%)	
	little	5 (14%)	4 (12%)	5 (17%)	
	some	6 (17%)	15 (44%)	9 (31%)	
	many	8 (22%)	8 (23%)	5 (17%)	
	unacceptable	2 (5%)	2 (6%)	2 (7%)	

DISCUSSION

Although we hypothesized that a more intensive follow-up regimen would lead to better medication adherence by increased support in the initial phase of pharmacological treatment, including a possibility to modify the prescribed therapy at an earlier phase, we did not find differences in adherence patterns between the study groups. An explanation might be that the content of follow-up contact is more important than the frequency of these contacts. The content of patients contacts was not controlled in this study. Secondly, intensified care might not be able to address all determinants that play a role in a complex behaviour as medication adherence. In other words, even when all health-care system related factors are optimized, patient-related, disease-related or socio-economic factors might still play an important role in adherence behaviour. These factors are not likely to be changed by an increased follow-up frequency.

There were no differences in patient satisfaction regarding medication, the care provided or the effect of chronic pain treatment between the study groups. However, satisfaction regarding the provision of information did significantly differ over time: a negative change in the standard follow-up group compared to a positive change in both intervention groups. In the hospital-initiated follow-up group, this effect may be (partly) due to the increased number of contacts between patient and caregiver, in which additional information might have been acquired. However, this does not explain the changes in the patient-initiated care group, as the number of contacts were not increased compared to the standard care group. In both intervention groups, the psychological effect of additional care and support, even if provided on an on-demand basis, might play a role.

More than half of the patients suffered considerable side-effects. Side effects have been negatively associated with pain medication adherence.[14,15] In a post-hoc multivariate regression analysis entering randomization and side effects as co-variables, side effects were contributing

significantly to underuse (p=0.005) and non-adherence after 11 weeks of therapy (p=0.033). Side effects may be one of the clues of the high rates of non-adherence in chronic pain patients, especially in the initial phase of pharmacological pain treatment.

A disappointing finding was that pain intensities during the study did not improve, and that most patient satisfaction scores, although slightly positive, were far from optimal. Although most patients wanted to continue their therapy, the analgesic effects did not reach pre-conceived expectations. Although patient satisfaction scores regarding medical care were generally acceptable, satisfaction scores regarding the effects of medications were unsatisfactory. A reason for these findings may be that patients, and caregivers possibly as well, tend to overestimate the ability for pain medication to improve pain intensity and quality of life. Furthermore, the common presence of side effects further affects patients' perception of prescribed therapy. The fact that medication was not successful to relieve pain in many cases, stresses the importance to follow-up on patients to consider change or cessation of pharmacological therapy.

Intensified hospital-initiated follow-up consisted of an increased number of contacts compared to standard care, which might be a burden on health-care resources without evident clinical benefit. Patient-initiated follow-up did not, contrary to our expectations, lead to a significant increase in unplanned patient contacts. It must be kept in mind that we combined patient-initiated care with routine follow-up, as we thought it would be irresponsible to not systematically evaluate the effect of medication prescribed. Most other studies reporting patient-initiated care systems did incorporate an annual or biannual consultation as a safety-net in the intervention groups as well.[10] In the long course of therapy, patient-initiated therapy might be a good and cost-effective alternative for planned follow-up.[9-11] Another advantage of patient initiated care might be that time and efforts are spent to patients that actually need it.

An important limitation of our study is the relative short follow-up period of three months after prescription of pain medication. As chronic non-malignant pain therapy often involves chronic use of analgesics, a longer follow-up period, for example one year, in this study might have led to different results. Whereas the intensified follow-up strategy would not be sustainable for one year in clinical practice, the patient-initiated follow-up strategy would. A second limitation is that genuine patient-initiated care should lead to less planned contacts compared to standard care. Because of safety reasons, we chose to combine standard care with additional care on demand. Future studies should investigate the non-inferiority, or even superiority, of patient-initiated care outcomes during long-term pain therapy. A final consideration is that, although the majority of patients suffered from neuropathic pain, the study sample was a heterogeneous sample with different medications prescribed. However, with the exception of an association with opioid use and overuse of medication, associations between different types of medication and adherence behaviour have not been reported.[5]

In conclusion, intensive hospital-initiated follow-up of chronic pain patients or patient-initiated follow-up following prescription of pain medication did not result in better medication adherence compared to standard care. Although these strategies led to higher patients'

satisfaction regarding information provision, other satisfaction scores did not differ from standard care. Whereas a planned intensive follow-up strategy automatically led to increased number of contacts, and therefore costs, the patient-initiated follow-up strategy did not. As patient initiated follow-up is an upcoming care model in the management of other chronic diseases, it might be considered for chronic pain management as well.

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SUPPLEMENTAL MATERIAL

Table S1. Pain diagnoses

Pain Diagnosis	Standard care (N=40)	Intensive follow-up (N=40)	Patient Initiated follow-up (N=40)
Central pain	0 (0)	2 (5)	1 (2)
Polyneuropathy	4 (10)	7 (18)	9 (23)
Peripheral neuropathy	8 (20)	11 (28)	7 (18)
Post-herpetic neuralgia	2 (5)	1 (2)	0 (0)
Post-surgical neuralgia	2 (5)	6 (15)	3 (8)
Post-traumatic neuralgia	1 (2)	2 (5)	1 (2)
Other	3 (7)	2 (5)	2 (5)
Radiculopathy	16 (40)	13 (33)	7 (17)
Cervical	4 (10)	1 (2)	1 (2)
Thoracic	0 (0)	0 (0)	1 (2)
Lumbar (herniated disc/canal stenosis)	5 (13)	4 (10)	1 (2)
Lumbar (failed back surgery syndrome)	7 (17)	8 (20)	4 (10)
Facial Pain	2 (5)	3 (7)	1 (2)
Low Back Pain	4 (10)	3 (7)	6 (15)
CRPS	4 (10)	1 (2)	3 (8)
Fibromyalgia	1 (2)	0 (0)	4 (10)
Distal arthropathy	1 (2)	0 (0)	2 (5)

Table S2. Prescribed medications at 2 weeks follow up and 11 weeks follow-up.

	2 weeks			11 weeks		
	Standard care (n=40)	Intensive follow-up (n=40)	Patient initiated follow-up (n=40)	Standard care (n=37)	Intensive follow-up (n=34)	Patient initiated follow-up (n=30)
Non-opioids						
NSAIDs	3 (8)	3 (8)	1 (2)	1 (3)	2 (6)	1 (3)
Anti-convulsants	17 (42)	9 (22)	6 (15)	13 (35)	10 (29)	7 (23)
Anti-depressants	5 (12)	8 (20)	7 (18)	5 (13)	2 (6)	3 (10)
Other	3 (8)	1 (2)	2 (5)	4 (11)	0 (0)	1 (3)
Anti-convulsants & anti-depressants	2 (5)	2 (5)	1 (2)	3 (8)	3 (9)	2 (7)
Other combinations of non-opioids	1 (2)	1 (2)	1 (2)	1 (3)	1 (3)	0 (0)
Opioids						
Oxycodone/ Tapentadol/ Fentanyl/ Tramadol	3 (7)	5 (13)	8 (20)	6 (16)	9 (26)	7 (23)
Opioids and non-opioids						
Opioids & anticonvulsants	2 (5)	2 (5)	3 (8)	1 (3)	3 (9)	2 (7)
Opioids & antidepressants	1 (3)	4 (10)	2 (5)	3 (8)	2 (6)	1 (3)
Opioids & NSAIDs	2 (5)	1 (3)	3 (8)	0 (0)	1 (3)	3 (10)
Other combinations of opioids and non-opioids	1 (3)	4 (10)	6 (15)	0 (0)	1 (3)	3 (10)

Table S3. Type of medication and frequency of non-adherence at T2

	Opioids	**Non-opioids**	**p**
Non-adherence n (%)	10 (24)	9 (15)	0.27
Underuse n (%)	5 (12)	8 (14)	0.82
Overuse n (%)	7 (17)	1 (2)	0.006
	Anti-convulsants & anti-depressants	**Direct-acting pain medication**	
Non-adherence n (%)	11 (17)	8 (23)	0.49
Underuse n (%)	8 (12)	5 (14)	0.80
Overuse n (%)	4 (6)	4 (11)	0.36

CHAPTER 6

The relation between patients' attitudes towards pain medication and their medication adherence and treatment outcome in chronic pain patients: a prospective study.

Leon Timmerman
Dirk L. Stronks
George Groeneweg
Frank J.P.M. Huygen

Submitted

ABSTRACT

Background

Non-adherence to prescribed pain medication is common in chronic non-malignant pain patients. Beliefs about pain medication have been reported to be associated with non-adherence behaviour in cross-sectional studies. The aim of this study was to prospectively investigate the relation between patients' beliefs about pain medication and their medication adherence and treatment outcome.

Methods

Chronic non-malignant pain patients completed a baseline questionnaire including the 47-item Pain Medication Attitudes Questionnaire (PMAQ), consisting of seven subscales regarding beliefs on prescribed medication. After 11 weeks, medication underuse and overuse were assessed by self-report. In addition, patient satisfaction regarding the prescribed medication and the presence of side effects were assessed.

Results

One hundred thirty three participants completed the baseline questionnaire, and 99 patients completed the follow-up questionnaire after 11 weeks. Concerns over side effects at baseline were positively associated with underuse after 11 weeks. Perceived need was positively associated with overuse. Concerns over side effects and mistrust in the doctor at baseline were negatively associated with patient satisfaction regarding prescribed medication after 11 weeks, and concerns over side effects and concerns over withdrawal were positively associated with presence of side effects after 11 weeks. Forty-two percent of patients were satisfied with prescribed medication. Fifty-eight percent of patients were moderately to extremely bothered by side effects.

Conclusion

Attitudes and concerns towards pain medication are associated with adherence patterns and outcome parameters. In order to improve medication adherence and therapy outcome, patient beliefs about pain medication should be taken into account.

INTRODUCTION

The prescription of medication is fundamental to medical management of most long-term conditions, including chronic non-malignant pain. However, many patients do not take their medication as prescribed, representing a failure to translate potentially effective therapy into optimal outcomes for patients and society.[1]

Adherence to a medial regime is defined as the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider.[2] Nonadherent behaviour may be intentional, unintentional, or both. Unintentional nonadherence occurs when a patient wants to adhere but is unable to because of lack of capacity or resources. Intentional nonadherence involves a decisional process not to follow recommendations. Individual perceptions about disease severity or prescribed therapy can influence motivation to start or continue medication.[3,4] Beliefs about medication are a well-investigated determinant of medication adherence in many chronic conditions.[3,4] The individual balance between perceived necessity and concerns about medication (the 'Necessity-Concerns Framework') may explain intentional nonadherence and provides a target for adherence-improving interventions.[4]

Perceived necessity and concerns towards pain medication have also been described to be associated with adherence in chronic non-malignant pain patients.[5,6] Using the 47-item 'Pain Medication Attitudes Questionnaire (PMAQ), perceived need was associated with analgesic overuse among chronic pain patients, and concerns over addiction and side effects were associated with underuse of pain medication in chronic pain patients.[5] Recently, a 14-item version of the PMAQ showed similar results.[7]

Beliefs about medications for chronic disease have been described to be related to therapy outcome, for example in diabetes, possibly by their effect on medication adherence.[8] It is unknown whether this applies to chronic pain treatment outcomes as well.

Earlier cross-sectional studies reported a relationship between patients beliefs about pain medication and medication adherence. The aim of this study was to prospectively investigate the relation between initial patients' beliefs about pain medication and medication adherence patterns and treatment outcomes during follow-up.

METHODS

This study was part of a randomized clinical trial, in which the effect of three different follow-up strategies on medication adherence and treatment outcome were compared. Methods have been described in detail in a previous report. Briefly, this single-center randomized controlled trial was performed in a pain treatment center of a large general hospital in the Netherlands after approval of the medical ethics committee. All patients with non-malignant pain existing longer than 3 months who received a new analgesic prescription or who received additional

pain medication to an existing treatment regimen, were invited to participate. Participants had to be able to complete electronic questionnaires in the Dutch language. Patients receiving medication on an 'as needed' basis and patients younger than 18 years were excluded. All participants provided written informed consent.

Procedures

After receipt of informed consent an email was sent containing a link to the web-based baseline questionnaire. After eleven weeks, a follow-up questionnaire was sent.

Patients were randomized to one of the three study groups: (1) standard follow-up, which consisted of follow-up visits after 6 and 12 weeks; (2) intensified hospital-initiated follow-up, which consisted of standard follow-up and additional scheduled counselling by a specialized nurse after 3, 5, 8 and 10 weeks; or (3) patient-initiated follow-up, which consisted of standard follow-up and additional counselling at patients' request.

Outcome measures

Baseline data collected were: age, gender, level of education, mean and maximum pain intensity in the previous week (11-point numeric rating scale (NRS)), number of different medications and duration of pain symptoms. Patient attitudes and concerns about pain medication were measured with a Dutch translation of the 'Pain Medication Attitudes Questionnaire (PMAQ)', a 47-item validated survey measuring attitudes and concerns towards pain medication regarding seven subscales (perceived need, mistrust in the prescribing doctor, and concerns over side-effects, adverse scrutiny, withdrawal symptoms, addiction and tolerance).[5] The English questionnaire was translated forward by two persons, one of whom was not related to the study. Two other persons performed backward translation, one of whom was not related to the study and had English as his native language.

Medication adherence was measured 11 weeks after initiation of the new prescription. Adherence was measured by asking two questions. One question measured underuse of pain medication: 'You received a prescription for pain medication from your doctor. How often do you, intentionally or unintentionally, miss or skip a dose? '. The second question measured overuse of pain medication: 'How often do you take more medication than prescribed? Answers were given on a 6 point scale (0=never, 1=seldom, 2= once a month, 3=once a week, 4 more than once a week, not every day, 5=every day).

Also after 11 weeks, patient satisfaction with current medication was measured (1=very satisfied, 2=satisfied, 3=neither satisfied nor dissatisfied, 4=dissatisfied, 5=very dissatisfied) as part of a more extensive questionnaire, the Dutch translation of the Pain Treatment Satisfaction Scale (PTSS; MAPI institute, Lyon, France).[9] Because we did want to study the relationship between attitudes towards medication and satisfaction with this medication, we did not use the data of the other modules measuring satisfaction with other aspects of care. Furthermore,

the burden of side effects was registered (1=no side effects, 2=a little bothered, 3=moderately bothered, 4=quite bothered and 5= extremely bothered).

Data analysis

Underuse was defined as missing a dose every week up to every day. Overuse was defined as taking additional medication every week up to every day.

PMAQ items were rated on a 6-point numerical scale (0=never true to 5=always true). One missing value per subscale was accepted, in which case the mean score of valid item scores were used. For the regression analysis, overall satisfaction with current pain medication scores was dichotomized, considering scores of 3 and higher as 'not satisfied'. Side effects were dichotomized for the regression analysis as well, considering scores of 3 and higher as 'bothered by side effects'.

Statistical analysis

Descriptive statistics were used to determine the frequencies of the demographic variables and PMAQ scores and to describe measures of central tendency and dispersion dependent on the shape of their distribution. The Shapiro-Wilk test was used to analyse whether or not parameters were normally distributed. Normally distributed data are presented as mean (SD), not normally distributed data as median (IQR). Binary logistic regression analysis was used to evaluate the contribution of PMAQ-subscores to the prediction of adherence, treatment satisfaction and side effects 11 weeks after initiation of the newly prescribed medication. To prevent overfitting of the model, we performed univariate binary logistic regression analyses of PMAQ subscales. Only those parameters with a significance level of $p \leq 0.2$ were entered into the final multivariate stepwise binary logistic regression analysis (method Backward Wald) with a probability out of p=0.1. To prevent multicollinearity, pairwise correlations between the parameters to be entered into the final model were calculated. Of those with a bivariate correlation of $\geq$ 0.7 only the parameter with the highest univariate significance level was entered into the final model.

For all statistics, alpha was set at the traditional 0.05 level. All analyses were performed using IBM SPSS Statistics version 24 (SPSS, Inc, Chicago, IL).

RESULTS

From November 2014 up to November 2016, one hundred thirty-three patients completed the baseline questionnaire. After 11 weeks, 99 patients (75%) completed the study. Baseline characteristics of these patients are presented in table 1.

Table 1. Demographics

		n=99
Age (median (IQR))		60 (21)
Gender (n (%))	Male	36 (36)
	Female	63 (64)
Level of education (n(%))	Primary education	2 (2)
	Lower secondary education	28 (28.3)
	Upper secondary education	19 (19.2)
	Post-secondary non-tertiary education	39 (39.4)
	Tertiary education	11 (11,1)
Mean Pain intensity (NRS) baseline	median (IQR)	7.0 (2,0)
Max Pain intensity (NRS) baseline	median (IQR)	8.0 (2,0)
Number of different medications (n (%))	1	11 (11)
	2	6 (6)
	3	9 (9)
	4	16 (16)
	5 or more	57 (58)
Pain duration (n(%))	0-3 months	0 (0)
	3-6 months	10 (10)
	6-12 months	15 (15)
	1-2 years	16 (16)
	2-3 years	15 (15)
	3-5 years	10 (10)
	more than 5 years	33 (34)

There were no differences found between the study arms (standard follow-up, intensive hospital-initiated follow-up and patient-initiated follow up) regarding underuse of medication, overuse of medication, PTSS-modules (except satisfaction with information provided) and presence of side effects.

Patients' attitudes towards pain medication

Median scores (IQR) of the seven PMAQ subscales of study participants were as follows: concerns over addiction 1.2 (1.0); perceived need 2.6 (0.9); concerns over scrutiny 0.9(0.9); concerns over side effects 2.0 (0.9); concerns over tolerance 1.8 (1.1); mistrust in the prescriber 1.9 (0.8); concerns over withdrawal symptoms 1.3 (0.7) (figure 1).

Medication adherence, patient satisfaction and side effects

Underuse was reported by 13 (13.1%) patients and overuse by 8 (8.1%) patients. Patients' satisfaction scores with current medication were as follows: 8 (8.1%) patients were very satisfied, 34 (34.3%) patients were satisfied, 32 (32.2%) patients were neither satisfied nor dissatisfied, 20 (20.2%) patients were dissatisfied and 5 (5.1%) patients were very dissatisfied. Presence of side effects were scored as follows: 28 (28.3%) patients had no side effects, 14 (14.1%) were a little

bothered, 30 (30.3%) were moderately bothered, 21 (21.2%) were quite bothered and 6 (6.1%) patients were extremely bothered by side effects.

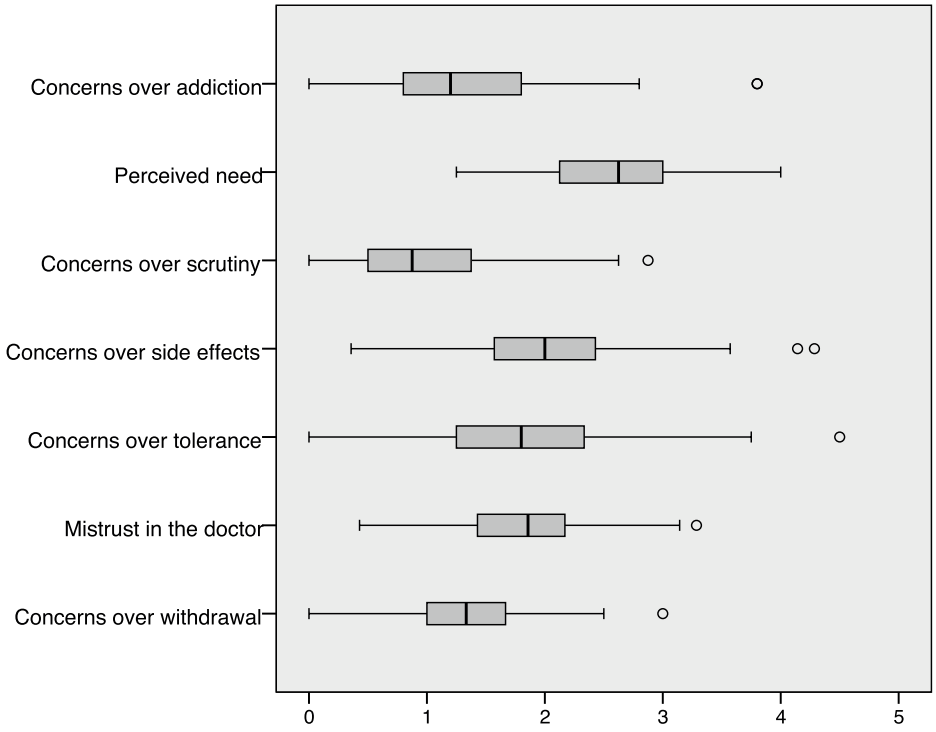

Figure 1. Boxplot of the subscales of the Pain Medication Attitudes Questionnaire scores (0=never true op to 5=always true).

Attitudes and concerns towards medication and underuse

The univariate binary logistic regression analyses revealed that only concerns over addiction (p=0.10), concerns over side effects (p=0.002) and concerns over withdrawal (p=0.027) significantly contributed to the prediction of medication underuse. Entering the above-mentioned parameters into the final multivariate binary logistic regression analysis resulted in a significant contribution of concerns over side effects to the prediction of medication underuse (p=0.003) (table 2A). The sensitivity (69.2%), specificity (80.7%), and overall classification (79.2%) were high using a cut-off value of 0.85. The ROC curve is presented in figure 2A.

Table 2A. Results of the multivariate binary logistic regression analysis of underuse.

		95% CI for Odds Ratio		
Included	B (SE) [p-value]	Lower	Odds Ratio	Upper
Constant	5.99 (1.51) [<0.001]			
Concerns over side effects	- 1.27 (0.43) [0.003]	0.12	0.28	0.65

Note: $R^2 = 0.10$ (Cox & Schnell), 0.18 (Nagelkerke). Model $\chi^2_{(1)} = 9.98$, p=0.002

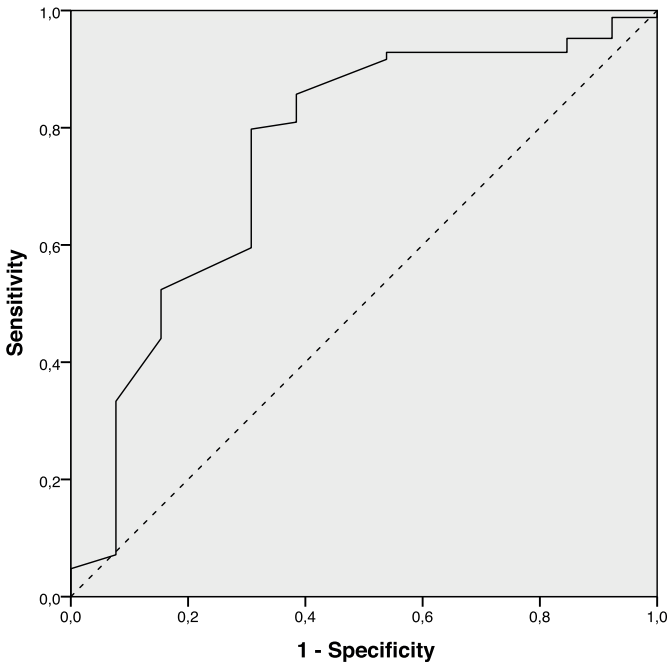

Figure 2A. Receiver operating characteristic curve of concerns over side effects as a predictor of underuse non-adherence (underuse versus no underuse). Area under the curve 0.754 (SE 0.079), p=0.003.

Attitudes and concerns towards medication and overuse

Both perceived need (p=0.015) and concerns over side effects (p=0.128) significantly contributed to the prediction of overuse in the univariate logistic regression. In the final multivariate analysis, only perceived need significantly contributed to the prediction of medication overuse (p=0.015) with a sensitivity of 62,5%, specificity of 87,5% and overall classification of 85,5% using a cut off value of 0.92 (table 2B). The ROC curve is presented in figure 2B.

Table 2B. Results of the multivariate binary logistic regression analysis of overuse.

		95% CI for Odds Ratio		
Included	B (SE) [p-value]	Lower	Odds Ratio	Upper
Constant	10.53 (3.53) [0.003]			
Perceived Need	- 2.08(0.87) [0.015]	0.02	0.12	0.66

Note: R^2 = 0.08 (Cox & Schnell), 0.18 (Nagelkerke). Model $\chi^2_{(1)}$ = 7,70, p=0.006

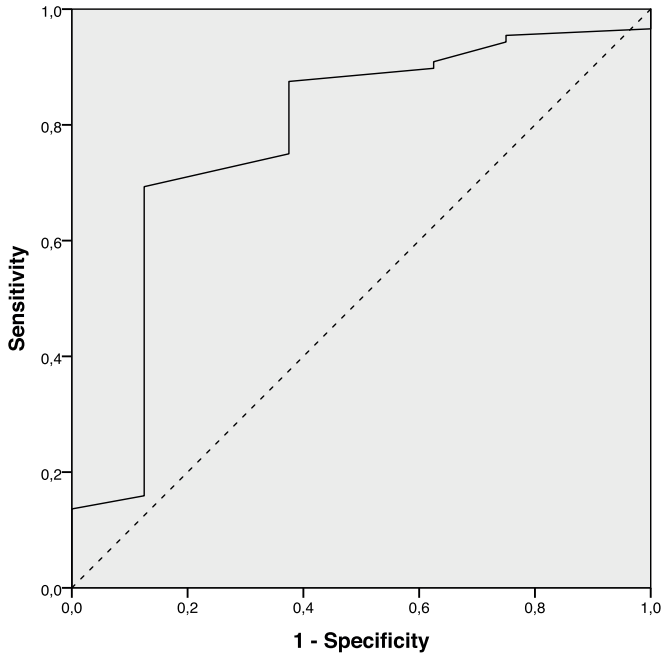

Figure 2B. Receiver operating characteristic curve of perceived need as a predictor of overuse non-adherence (overuse versus no overuse). Area under the curve 0.776 (SE 0.094), p=0.01.

Attitudes towards pain medication and satisfaction with medication

Concerns over scrutiny (p=0.11), concerns over side effects (p=0.07), concerns over tolerance (p=0.07), mistrust in the doctor (0.05), concerns over withdrawal (p=0.037) were significantly associated with satisfaction with prescribed medication in the univariate analysis. Entering these items into the multivariate analysis resulted in a significant contribution of mistrust in the prescribing doctor (p=0.035) and concerns over side effects (p=0.076) to the prediction of satisfaction (sensitivity 77,4%, specificity 52,4% and overall classification of 66,3% with a cut of value of 0.5) (table 2C). The ROC curve is presented in figure 2C.

Table 2C. Results of the multivariate binary logistic regression analysis of satisfaction about prescribed medication.

		95% CI for Odds Ratio		
Included	B (SE) [p-value]	Lower	Odds Ratio	Upper
Constant	4.27 (1.69) [0.011]			
Concerns over side effects	- 0.54 (0.30) [0.076]	0.32	0.58	1.06
Mistrust in the doctor	- 1.01 (0.48) [0.035]	0.14	0.36	0.93

Note: $R^2 = 0.08$ (Cox & Schnell), 0.11 (Nagelkerke). Model $\chi^2_{(2)} = 8{,}11$, p=0.017

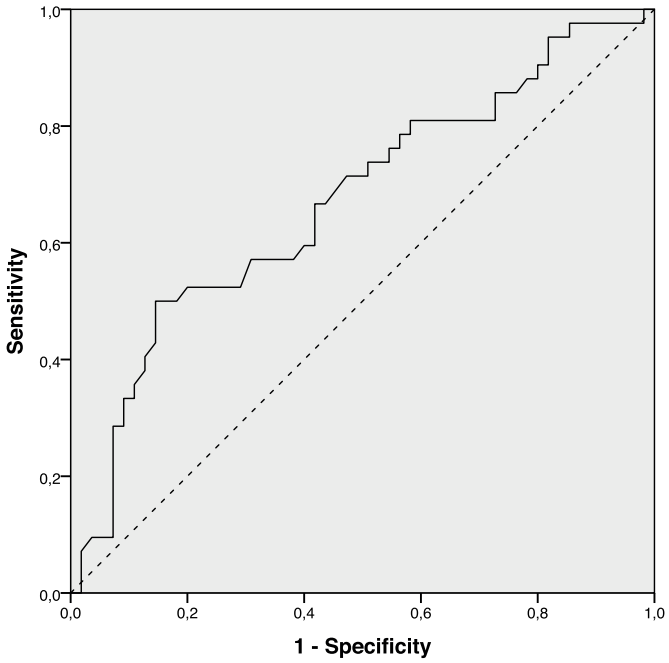

Figure 2C. Receiver operating characteristic curve of concerns over side effects and mistrust in the doctor as a predictor of patient satisfaction about prescribed medication (satisfied versus not satisfied). Area under the curve 0.671 (SE 0.056), p=0.04.

Attitudes towards pain medication and presence of side effects

Concerns over scrutiny (p=0.121), concerns over side effects (p=0.005), concerns over withdrawal (p=0.022), mistrust in the doctor (p=0.141) and concerns over tolerance (p=0.082) were associated with the presence of side effects after 11 weeks. Entering these items into the multivariate analysis resulted in a significant contribution of concerns over side effects (p=0.032) and concerns over withdrawal (p=0.10) to the prediction of side effects after 11 weeks (sensitivity 65,5%, specificity 63,4% and overall classification of 64,6% with a cut of value of 0.55) (table 2D). The ROC curve is presented in figure 2D.

Table 2D. Results of the multivariate binary logistic regression analysis of presence of side effects.

		95% CI for Odds Ratio		
Included	B (SE) [p-value]	Lower	Odds Ratio	Upper
Constant	- 3.30 (1,20) [0.006]			
Concerns over side effects	0.71 (0.34) [0.035]	1.05	2.04	3.96
Concerns over withdrawal	0.64 (0.38) [0.094]	0.90	1.90	4.01

Note: R^2 = 0.11 (Cox & Schnell), 0.14 (Nagelkerke). Model $\chi^2_{(2)}$ = 10.61, p=0.005

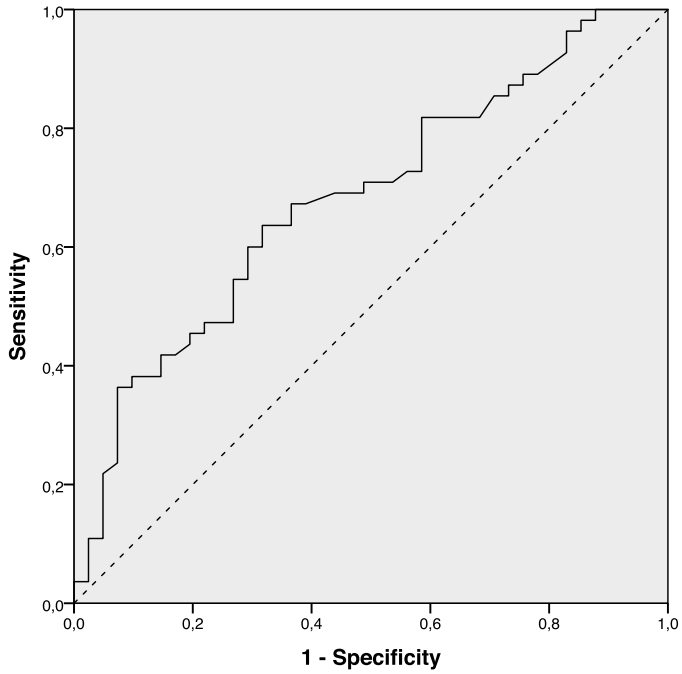

Figure 2D. Receiver operating characteristics curve of concerns over side effects and concerns over withdrawal as a predictor of side effects (side effects versus no side effects). Area under the curve 0.681 (SE 0.054), p=0.002.

DISCUSSION

This prospective study confirms results of earlier cross-sectional studies, in which associations were found between patient beliefs about prescribed medication and medication adherence.[5] As previously discussed, underuse and overuse are two different entities that should be considered separately.[6,10] This is confirmed by the fact that different beliefs about medication contribute to these behaviours. Underuse non-adherence was associated with concerns over side effects of pain medication. This effect was independent of the actual presence of side effects, as verified by a post-hoc binary regression analysis entering concerns over side effects

(p=0.024) and presence of side effects (p=0.030) as covariates. Overuse non-adherence was associated with perceived need for pain medication. In the earlier study in which the PMAQ was used in secondary care, other PMAQ subscales were demonstrated to be associated with underuse (concerns over withdrawal, perceived need) and overuse (concerns over scrutiny) as well.[5] Although directions of the associations were similar, these factors did not reach significance in our study. A possible explanation might be the different definition of underuse and overuse. Instead of considering any deviation from the prescription as nonadherence, in our study patients were allowed to deviate from the prescription up to once a week to be considered adherent.

Negative beliefs and concerns about pain medication during initiation of pharmacological therapy were related to treatment outcome. Mistrust in the doctor was negatively associated with patient satisfaction with prescribed medication. Initial mistrust seems to have an effect on satisfaction after three months, indicating the importance of building on a good patient-provider relationship from the initial visit onwards. Patient education, shared decision making, and affective communication are behaviours that might enhance the relationship and thereby, treatment effectivity. Concerns over side effects during initiation of therapy were negatively associated with satisfaction with prescribed medication. This finding is not surprising, as concerns over side effects predicted the actual presence of side effects. Side effects are well known to have an important negative impact on treatment outcome of pharmacological pain therapy.

The finding that patients' concerns over side effects were associated with presence of side effects after 11 weeks, might be explained by earlier negative experiences with pain medication. Chronic pain patients referred to secondary care have often been treated with medications before. Side effects may not only occur due to intolerance to a specific drug, but also due to impaired drug metabolism caused by decreased liver or renal function, or due to interactions with other medications. For this reason, patients with earlier negative effects of pain medication might be more susceptible for repeated suffering from side effects. However, another explanation might be that patients who are worried about side effects of medication are more alert to detect and suffer from negative effects of medications.

The non-adherence levels found in this study were lower than reported in earlier studies. Firstly, this might be due to the measurement of adherence we selected consisting of one question regarding underuse and one regarding overuse of medication. Although it was used anonymously, and patients did not have a reason to report different than their actual medication use, this self-report measure is susceptible to overestimation of adherence, because of social desirability and memory biases.[11] Secondly, patients were allowed to deviate from the prescription up to once a week to be considered adherent. Other studies use a more strict definition of non-adherence as 'any deviation of prescribed therapy'. Up to now, there is no generally accepted definition of adherence and no general accepted subjective or objective operationalisation of this concept. We chose this self-report measure because it is clinically

applicable, and this definition because it seems unrealistic to expect patient to never, intentionally or unintentionally, omit or add a dose.

Findings about associations between patient views about medication and medication adherence are clinically relevant and should support the design of future adherence-improving interventions. Taking account of patients' necessity beliefs and concerns about pain medication when prescribing new analgesics could enhance adherence to these prescriptions. The first step in facilitating adherence is to take a 'no-blame approach' and encourage an honest and open discussion to identify barriers to adherence.[12] Individual beliefs and concerns should be addressed, leading to a shared decision regarding pharmacological therapy. This approach, which has had encouraging results [13], might lead to alternate (or no) treatment when specific barriers are too strong to overcome. The most challenging reality is that thorough assessment and discussion of patients' views about medication costs significant time, and is difficult to achieve during a busy schedule at a pain clinic. Given the finding that physicians generally take less than a minute to prescribe new medication, there is a need for change.[14] Questionnaires as the PMAQ, of which a shorter 14-item form has been introduced recently, might serve as a starting point for discussions about pain medication. Although standardized education might increase patient knowledge, tailored counselling is necessary to address specific concerns that are highly individual.[15]

A limitation of this study might have been the fact that it is a sub-study within a randomized trial which investigated the effect of different follow-up strategies on medication adherence and pain treatment satisfaction. However, the study allocation did not contribute to any of the outcome parameters used in this study. Furthermore, in a post-hoc analysis (data not shown), we entered randomization as a covariate, with identical results of the multivariate regression analysis. Secondly, the follow-up period after initiation of chronic pain therapy in this study was only eleven weeks, which may account for the relatively low non-adherence rates. It is likely that non-adherence rates would have been higher after, for example, six months. A final limitation is the dropout rate of 25%, for which the reasons were not recorded. Patients wo do not adhere to a study protocol which consists of the completion of three questionnaires might have different medication adherence patterns as well.

In conclusion, this study prospectively confirms earlier cross-sectional reports about the association between attitudes towards prescribed pain medication and non-adherence patterns. Furthermore, attitudes and concerns towards pain medication were related to outcome parameters. In order to improve medication adherence and therapy outcome, patient beliefs about pain medication should be addressed.

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CHAPTER 7

The design of a theory based intervention to improve medication adherence in chronic pain patients.

Leon Timmerman
Dirk L Stronks
Frank JPM Huygen

Curr Med Res Opin. 2017 Jul; 33:1293-1301

ABSTRACT

Objective

Non-adherence to pain medication is common in chronic pain patients and may result in unfavorable treatment outcome. Interventions to improve adherence behavior often fail to significantly change medication use. In this report we describe the application of a theoretical psychological model of behavior change in order to design an intervention to improve medication adherence in chronic pain patients.

Methods

This study applies the Behavior Change Wheel framework and the Behavior Change Techniques Taxonomy to design a theory-based intervention to improve pain medication use. Available literature was used to extract determinants of adherence in chronic pain patients.

Results

Selected target behaviors to improve medication adherence are: share agreement on follow up policy, monitor medication adherence, provide patient education routinely, discuss attitudes and concerns towards pain medication, develop medication taking habits and use medication reminders. The intervention consists of three components in which relevant behavior change techniques are applied: (1) changes in the electronic patient data management systems to enable medical staff to apply target behaviors; (2) bi-annual education of medical staff to commit the team to the proposed intervention and provide feedback; (3) routine and mandatory education of chronic pain patients following prescription of pain medication.

Conclusions

To improve medication adherence in chronic pain patients, most interventions should be focused on providers of pain therapy. Prescribing chronic pain medication should be seen as part of a larger treatment regimen including adequate follow-up, adherence monitoring and patient education during the course of treatment.

INTRODUCTION

Chronic pain is a common medical condition affecting approximately 20 percent of the European adult population.[1] In addition to the physical and emotional burden it brings, the financial cost to society is huge, currently estimated at more than €200 billion per annum in Europe and $150 billion per annum in the USA.[2] Although treatment often requires a multidisciplinary approach, pharmacological treatment remains one of the cornerstones of chronic pain management. However, the response to chronic drug treatment is often poor and highly variable.[3] There are several variables reasons for this variability. Age, gender, ethnicity and actual level of stress, mood or diseases may modify pain perception, and pharmaco-genetic differences result in a variable response to pain medication.[4] Non-adherence to pain medication is also thought to play a role in the sub-optimal effect of analgesic therapy. Up to 40% of chronic pain patients do not use their medication as prescribed.[5,6] Non-adherence in other types of chronic diseases resulted in reduced clinical benefit, avoidable morbidity and mortality, medication wastage and increased medical costs.[7] Furthermore, it could bias the assessment of treatment efficacy. The consequences of non-adherence in chronic pain patients are less clear. An association between pain medication adherence and treatment outcome has been shown, but a causal relationship has never been demonstrated.[8] However, it seems plausible that some degree of pain medication adherence is necessary to maximize treatment effect and reduce the burden of side-effects as well.

Interventions designed to improve medication adherence in chronic disease have mostly been described to be ineffective or very complex, making it difficult to be carried out in a non-research setting.[9] Most of these interventions were developed without a sound theoretical base. Although medication adherence research has provided several factors associated with adherence, the application of these data to improve medication taking is limited.

Theoretical psychological models explaining human behavior provide insight in the mechanisms involved in behavior change.[10] In this study, we use the 'Behavior Change Wheel' (BCW) framework as a systematic approach to propose an intervention designed to improve medication adherence (figure 1).[11,12] The BCW is designed to move from a behavioral analysis of the problem to evidence-based intervention design. Incorporated in this approach is the COM-B model of behavior that makes it possible to identify what needs to change in terms of capability (C), opportunity (O) and motivation (M), to actually achieve the desired behavioral change.[12] Complementing the BCW framework is the Behavior Change Techniques Taxonomy. The taxonomy describes 93 specific behavior change techniques and allows for standardized reporting of interventions.

The aim of this study was to design a theory-based, practicable intervention to improve medication adherence in chronic non-malignant pain patients.

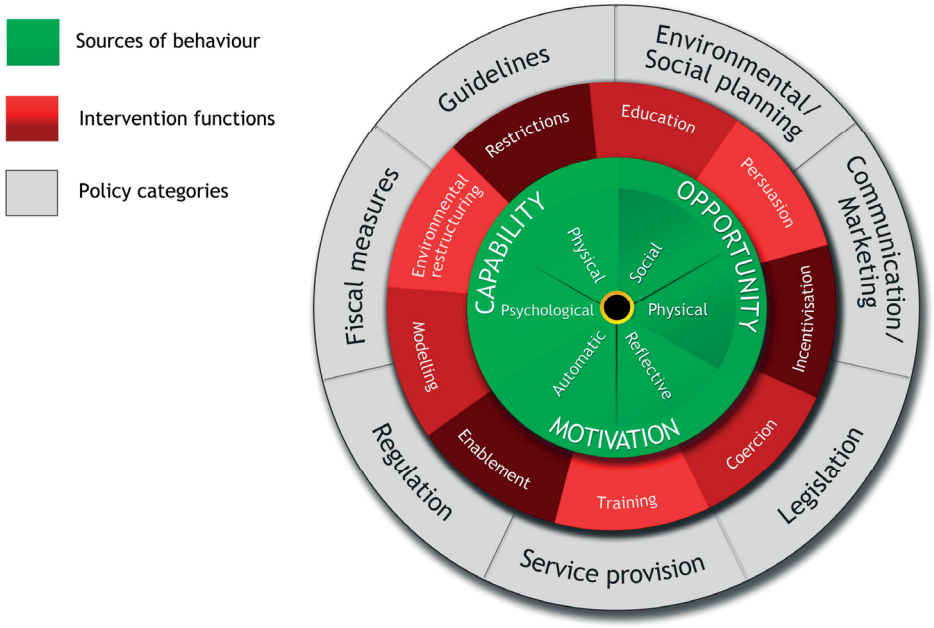

Figure 1. The behavior change wheel. From: Michie, van Straalen, West, 2011.[10] Licensed under CC BY (https://creativecommons.org/licenses/by/2.0/).

THE INTERVENTION DESIGNING PROCESS

Application of the BCW framework is outlined in a guidebook that contains a series of worksheets based on eight steps.[11] The process involved three stages encompassing the eight distinct steps (figure 2). The initial step in this approach is to *identify the problem behavior* (1), followed by *selection of target behaviors,* i.e. behaviors to be changed (2). The selection is based upon relevant scientific evidence. Target behaviors have to be specified as much as possible (3). The next step is to *analyze what needs to change* using the COM-B model: e.g., is greater Capability, more Opportunity and/or stronger Motivation required (4)? Having identified this, the BCW is used to analyze *how to achieve these changes*, e.g. by education, training or environmental changes (5). Then, what *policies*, e.g. legislation or service provision, might facilities these changes (6). The following step is to select the 'active ingredients', from the behavior change techniques taxonomyV1 containing 93 techniques to change behavior (7).[13] Finally, the best way to *deliver the intervention* has to be chosen, e.g. by face-to-face contact or mass-media campaign, once or repeatedly (8).

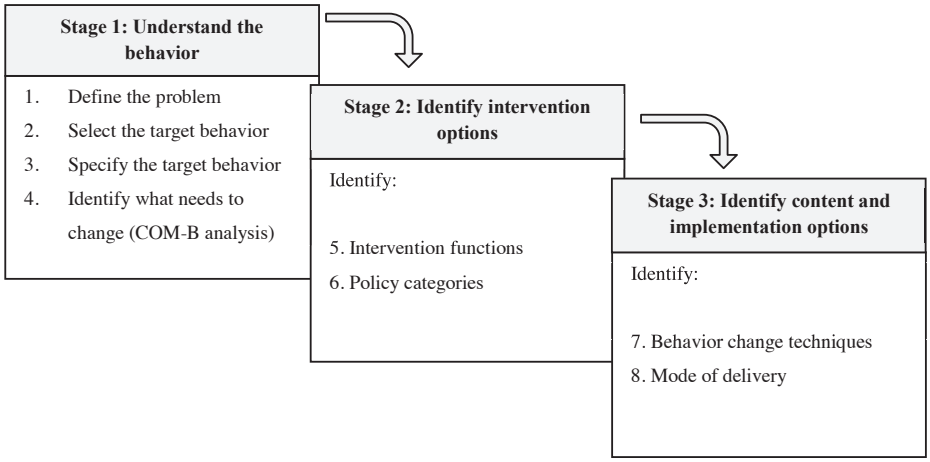

Figure 2. The intervention design process. From: Michie, Atkins and West, 2014.[11] Licensed under CC-BY (http://creativecommons.org/licenses/by/4.0/).

At the center of the BCW framework is the COM-B model (figure 3).[12] This model recognizes that each behavior is the result of an interaction between its behavioral components, namely capability, opportunity and motivation. It can provide explanations why specific recommended behaviors are not engaged in. Changing behavior will involve changing one or more of these components and its sub-components:

- Capability, the individuals capacity to engage in the behavior, is subdivided into *physical capability* (physical skills or strength for a behavior) and *psychological capability* (psychological skills or knowledge to perform behavior).
- Motivation, all brain processes that energize and direct behavior, is subdivided into *reflective motivation* (conscious processes involving plans and evaluations) and *automatic motivation* (automatic processes involved in performing behavior, such as habits and emotional responses).
- Opportunity, all factors lying outside the patient that make performance of the behavior possible or prompt it, is subdivided into *physical opportunity* (opportunity provided by the environment, including time and resources), and *social opportunity* (opportunity afforded by interpersonal influences).

1. Identification of the problem behavior

The problem behavior is non-adherence to prescribed pain medication in chronic pain patients. As medication adherence was defined as 'taking medication as prescribed' the intervention to be proposed is intended to address both underuse and overuse of pain medication. Aberrant use or abuse of pain medication falls outside the scope of this study, as it is a separate problem behavior with its own separate risk factors. As different medications are associated with differ-

ent adverse effects and patient concerns, the intervention should be able to address the differences between, for example, opioids, anticonvulsants and NSAIDs. In addition, the intervention should primarily fit within the context of a secondary pain treatment center.

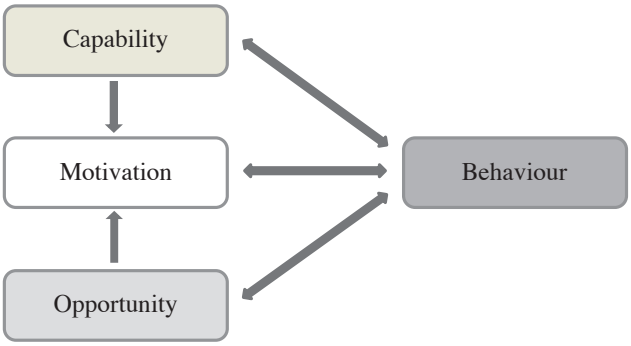

Figure 3. The COM-B model of behavior. From: Michie, van Straalen, West, 2011.[10] Licensed under CC BY (https://creativecommons.org/licenses/by/2.0/).

2. Selection of target behaviors

Earlier, we performed a systematic literature review to identify determinants of medication adherence in chronic pain patients.[6] In this review, determinants were extracted from 19 studies. Four independent pain physicians (including the first author) translated this determinants into potential target behaviors that might improve medication adherence (table 1). These potential target behaviors were judged on their likelihood to have an impact on adherence, the likelihood that the behavior can actually be performed, the possibility that the behavior has an impact on other (target) behaviors (spillover score), and the possibility to measure the behavior. Judging resulted in a rating of each item as very promising, promising , unpromising but worth considering or as unacceptable. Secondly, discrepancies were discussed until consensus was reached. Finally, most promising target behaviors to improve adherence were selected in this consensus meeting (supplemental table S1).

Final selected target behaviors:

- *Shared agreement on follow-up policy*, i.e. a clear and documented follow-up agreement that corresponds with individual patient expectations during analgesic treatment, was judged a reasonable target to improve a doctor-patient relationship (e.g. 'shall we discuss the effect of your medication within four weeks?', 'would you prefer to call or visit the hospital?').
- *Active monitoring and recording medication adherence*, and communicating to do so, was considered a second target that has shown its benefit in earlier studies.[14]
- *Patient education* to provide necessary knowledge of chronic pain and analgesic treatment and *discussion of individual attitudes and concerns* ('what do you think about taking pain

medication?') about pain medication were selected as target behaviors of health care providers. Several patient factors have been reported to predict adherence behavior.[6] The way people think about their condition and proposed therapy, including specific fears and concerns towards prescribed therapy have been consistently associated with adherence behavior.[15,16]

- In patients, the *formation of habits* and the *use of reminders to take medication* were chosen target behaviors. Reminders have been previously reported to improve medication adherence.[17]

Table 1. Determinants of pain medication adherence and potential target behaviors to change adherence behavior. Target behaviors judged most promising are presented in bold.

Determinants of Pain Medication Adherence	Potential Target behaviors
- Age	
- Pain Intensity	
- Active coping strategies	
- Dosing frequency	- Avoid high dosing frequency
- Polymedication	- Avoid polymedication
- Psychiatric disease	- Rethink prescribing pain medication in psychiatric patients
- History of drug abuse	- Rethink prescribing pain medication in patients with a history of drug abuse
- Quality of patient-caregiver relationship	- Optimize patient caregiver relationship by routinely: • Share decision making • Define goal and time frame to reach goal • **Share agreement on follow up policy**
- Active adherence monitoring strategies	- **Monitor medication adherence**
- Knowledge and perceptions of disease severity	- **Educate patients**
- Knowledge, attitudes and concerns towards pain medication • perceived need for pain medication • fear of withdrawal symptoms • fear of addiction • fear of side effects • fear of adverse scrutiny	- **Educate patients** - **Address and discuss attitudes and concerns towards pain medication**
- Stimuli or cues to take medication (daily)	- **Habit formation** - **Use reminders to use medication** - Self-monitoring of adherence

Other potential target behaviors were considered less promising. Although *shared decision making* concerning medical treatment might improve the doctor-patient relationship and thereby support adherence, it seems difficult to realize and measure this in each individual patient-doctor consultation. The same holds true for '*defining goal and time frame to reach goal*'. The *avoidance of high dosing frequency* might be difficult to achieve as well, and the *avoidance of polymedication* is frequently impossible because of comorbidity. Although alertness is justified, it is not possible to *refrain from prescribing pain medication to all patients with a history of psychological distress or alcohol abuse*, as this is a common situation in chronic pain patients. *Self-monitoring* was considered as a promising behavior in patients, but was not chosen as a

target because chronic persistence of this behavior, for example the use of a medication diary during a period of several months, is unlikely.

3. Specification of target behaviors

The selected target behaviors were specified as much as possible (see table 2).

Table 2. Specification of target behavior

Target behavior	Who needs to perform the behavior?	What do they have to do differently to achieve the desired behavior?	When do they need to do it?	Where do they need to do it?	How often do they need to do it?	With whom do they need to do it?
Share agreement on follow up policy	Medical Staff	Agree and record how and how often follow up will take place.	After each contact	In the hospital, on the phone or by email.	After each contact	With the patient
Monitor medication adherence	Medical Staff	Ask specifically about medication use	During each contact	In the hospital, on the phone or by email	During each contact	With the patient
Educate Patients	Medical staff	Organize educational interventions	After initiating pharmacological pain therapy	In the hospital	Once a month	Patients have to attend educational sessions
Discuss attitudes and concerns towards pain medication	Medical staff	Actively discuss and register attitudes and concerns towards pain medication	During each contact	In the hospital	During each contact	With the patient
Habit formation	Patient	Combine medication taking with other automated habits (e.g. tooth brushing)	After initiating pain medication	At home	Always	Not dependent on others
Use reminders to take medication	Patient	Use any reminder to prevent forgetting medication	After initiating pain medication	Everywhere	Always	Not dependent on others

4. COM-B analysis: identify what needs to change

The next step was to use the COM-B model to analyze whether the targets of the interventions, caregivers and patients in this case, have the capability, opportunity and motivation to carry out the selected behaviors. In this step, a behavioral diagnosis for each target behavior was made by selecting COM-B components that need change to reach this behavior. This step was performed by four independent clinicians (including the first author) during a second consensus meeting.

In caregivers, *psychological capability* has to change by improving their relevant knowledge and skills to discuss medication use and apply adherence improving interventions. Every health care provider has to be aware of the magnitude of the problem of non-adherence and the importance of their efforts to optimize medication use. As interventions cost time and effort, *reflective motivation* is an important component to be maximized, as doctors should have the intention to apply the intervention consistently. *Physical opportunity* has to change to create a context in which the target behaviors can be performed easily (e.g. more time available for each patient visit; changes in patient data collection to ensure adequate attention for medication adherence). *Social opportunity* might need to be changed to apply selected interventions uniformly across a department to maximize the effects. This might, for example, be achieved by peer support. *Automatic motivation* needs to change to consistently ensure intervention application and create new routines.

In chronic pain patients, to support target behavior, some behavioral components might be changed. *Psychological capability* to use medication consequently with help of reminders and clues should be optimized. *Reflective motivation* to take medication regularly and to use reminders consequently might need change. Associative learning using reminders and clues might induce *automatic motivation.* Finally, *physical opportunity*, consisting of resources to apply reminders (stickers, smartphone applications), is needed.

5. Identification of intervention functions: how to achieve change?

This step, and all following steps, were performed by the authors, consisting of clinicians and a psychologist (DLS). Intervention functions considered in the BCW are: education, persuasion, incentivisation (e.g. by means of a reward), coercion, training, restriction, environmental restructuring (including changes in time schedules etc.), modelling (providing an example) and enablement (make it easier to perform a behavior). To make sure that proposed interventions would not only lead to a theoretical exercise but could actually applied in clinical practice, all intervention functions were evaluated with the APEASE criteria: Affordability, Practicability, (cost-) Effectiveness, acceptability, safety and equity (does the intervention type increase or decrease disparities between societal groups?). As we distinguished between target behaviors of medical staff and those of patients, so we also distinguished between intervention functions aimed at behavior change of the medical staff and that of patients.

According to us, the most relevant functions to change caregivers behaviors are *education* of caregivers about the importance of adherence and relevant interventions to support adherence and *persuasion* to perform the selected target behaviors. Furthermore *environmental restructuring* and *enablement* (e.g. by means of time, electronic aids) should support the performance of adherence improving behaviors and strengthen reflective and, eventually, automatic motivation of healthcare providers. *Training* how to perform adherence improving behaviors would be helpful, but is not practicable there is not enough time for all staff members to follow training sessions.

In patients, we think that all intervention functions might generate the desired target behaviors (i.e., habit formation, use of reminders). The most relevant were patient *education* and *persuasion* to increase psychological capability and motivation to perform target behaviors, *environmental restructuring* and *enablement* to maximize automatic motivation to adhere to prescribed therapy. The use of *coercion* was considered unacceptable, and *incentivisation* was considered impracticable and not affordable on a large scale.

6 . Identification of policy categories

In the next step, the BCW was used to select appropriate policy categories for each intervention function selected: what policies would enable the selected intervention functions to occur? Policy categories (legislation, service provision, regulation, fiscal measures, guidelines, communication and marketing, environmental and social planning) were evaluated with the APEASE criteria.

Policy selection depend upon the extend in which the interventions will be introduced: in one hospital or on a larger scale. Initially, the intervention should be evaluated on a small scale. The implementation should be *communicated* to the caregivers involved, and departmental *guidelines* about pharmacological pain therapy may support the performance of target behaviors. *Provision of educational services* for caregivers and patients are likely to be appropriate to increase capability and motivation. Finally, *environmental planning* consisting of changes in patient data management systems, scheduling of patient visits and introduction of reminder services, should be considered.

7. Identification of behavior change techniques

The authors discussed 93 items of the behavior change techniques taxonomyV1 (see also the smartphone app 'BCTs taxonomy' created by the 'Center for Behavior Change' of the University College London) and selected most relevant items from to be incorporated in the interventions.

For medical staff, we would suggest that improved psychological capability can be achieved by *information about consequences* of performing a target behavior (e.g. monitoring medication adherence), preferably from a *credible source*. Instruction on how to perform this behavior, *goal setting* (e.g. significant reduction of non-adherence within a year) and action planning (e.g. register adherence for every patient using analgesics from now on) regarding the intervention components might be applied. Physical opportunity may be improved by *adding objects, prompt or cues to the 'environment'* (most importantly within the electronic patient data management system). Social opportunity might be improved by *sharing commitment* to the intervention with the entire health care team, including all senior staff members. Reflective motivation can be positively changed by sharing *information about consequences* of a preferred behavior, *feedback on behavior*, including its consequences. Most ideally, positive feedback (about reduction of non-adherence levels) following performance of target behaviors would stimulate persistence of these behaviors. Furthermore, reflective motivation should benefit

from enabling techniques that make the intervention easy to perform by *changing the environment* of caregivers. When an intervention is difficult to perform, persistent use will be unlikely in daily practice. Automatic motivation will benefit from BCTs such as *habit formation* and the *addition of prompts and cues* to the (electronic) environment.

For patients, physical and psychological capability to form medication taking habits and use reminders to achieve this, can be improved by *providing information about the consequences* of the behavior, *setting goals* about medication adherence and *providing instructions* on how to use reminder tools and how to form habits. Physical opportunity should benefit from changes in the patients' environment e.g. *addition of cues* to take medication or reminders using smartphone applications, that a readily available nowadays. Social opportunity to take medication regularly might increase by *support from family or relatives*. Reflective motivation requires *information about consequences* of medication. Automatic motivation requires the *formation of medication taking habits*, possibly supported by *prompts or clues* or other environmental changes. Finally, strong *commitment* to start, continue or restart the attempt to take the medication as prescribed is a prerequisite for medication adherence.

8. Identification of modes of delivery

After identifying intervention content and policies for implementation, suitable modes of delivery (face-to-face delivery, for example group or individual counselling, or distant delivery, ranging from individual phone contact to large marketing campaigns) were selected by the authors for all parts of the intervention:

Hospital staff

Mode of delivery: **face to face group sessions** to educate and persuade prescribing health care providers to perform the target behaviors: *share agreement on follow up; monitor medication adherence; educate patients; discuss attitudes and concerns towards pain medication* by using the behavior change techniques as described above. **Distant individual-level** delivery of behavior change techniques might include required fields in the patient file regarding adherence measurement and follow-up strategy. Furthermore, a prompt might be added to invite patients to pain education. Finally, target behaviors might be enabled by scheduling more time per patient. At **distance population-level**, providing educational and scientific articles about the importance of pain medication adherence might increase awareness of specific interventions. Clinical guidelines may suggest to restrict prescribing to patients that accept and receive education and adherence monitoring.

Patients

Mode of delivery: **face to face group sessions** to educate and persuade patients to form habits of medication taking. **Distant individual-level** delivery of prompts/cues by SMS-reminders.

Another distant delivery to enable habit formation might be providing stickers, posters with text such as 'did you take your medication?' which can be used at home.

INTERVENTION DESIGN

We followed the step-by-step approach of the intervention design process as described by Michie et al, applying the COM-B model to the behavior of non-adherence to pain medication. We conclude with an intervention design that meets the APEASE criteria (affordability, practicability, (cost-) effectiveness, acceptability, side-effects (safety) and equity).

The intervention consist of three parts, which are outlined in figure 4. First, prescribers should be informed and persuaded to preform adherence improving behaviors. Second, changes in patients data management systems should be made that maximally support these behaviors. Finally, patients receiving pain medication should be educated about their disease, its treatment, the importance of medication adherence and the use of tools to support adherence behavior.

DISCUSSION

We applied the methodology of 'the Behavior Change Wheel' in order to design a theory based intervention to improve medication adherence in chronic pain patients. Earlier attempts without thorough theoretical foundation have been shown to be unsuccessful.[18,19] As medication adherence is a complex behavior and chronic pain is a complex multifactorial disease, there are many factors that may play a role in non-adherence behavior. Therefore, interventions should be tailored, at least partially, to the individual patient.

After prioritizing and specifying target behaviors, making a behavioral diagnosis, identifying intervention functions, policy categories and behavior change techniques, there still remained multiple clues for interventions. Although this does not stroke with the 'less is more principle' as stated by the designers of the BCW, we wanted to propose an overarching intervention that included behavior change of patients as well as caregivers. The proposed intervention largely resembles strategies also described within the SIMPLE approach, a mnemonic for Simplifying regimen characteristics, Imparting knowledge, Modifying patient beliefs, Patient communication, Leaving the bias (of demographic factors) and Evaluating adherence.[20] The SIMPLE approach provide a simplistic overview of methodologically proven adherence-enhancing strategies in general pharmacological therapy. Obviously, although pain medication adherence in chronic pain patients is complex behavior in a complex and heterogeneous patient category, pain adherence interventions should be based on the same principles.

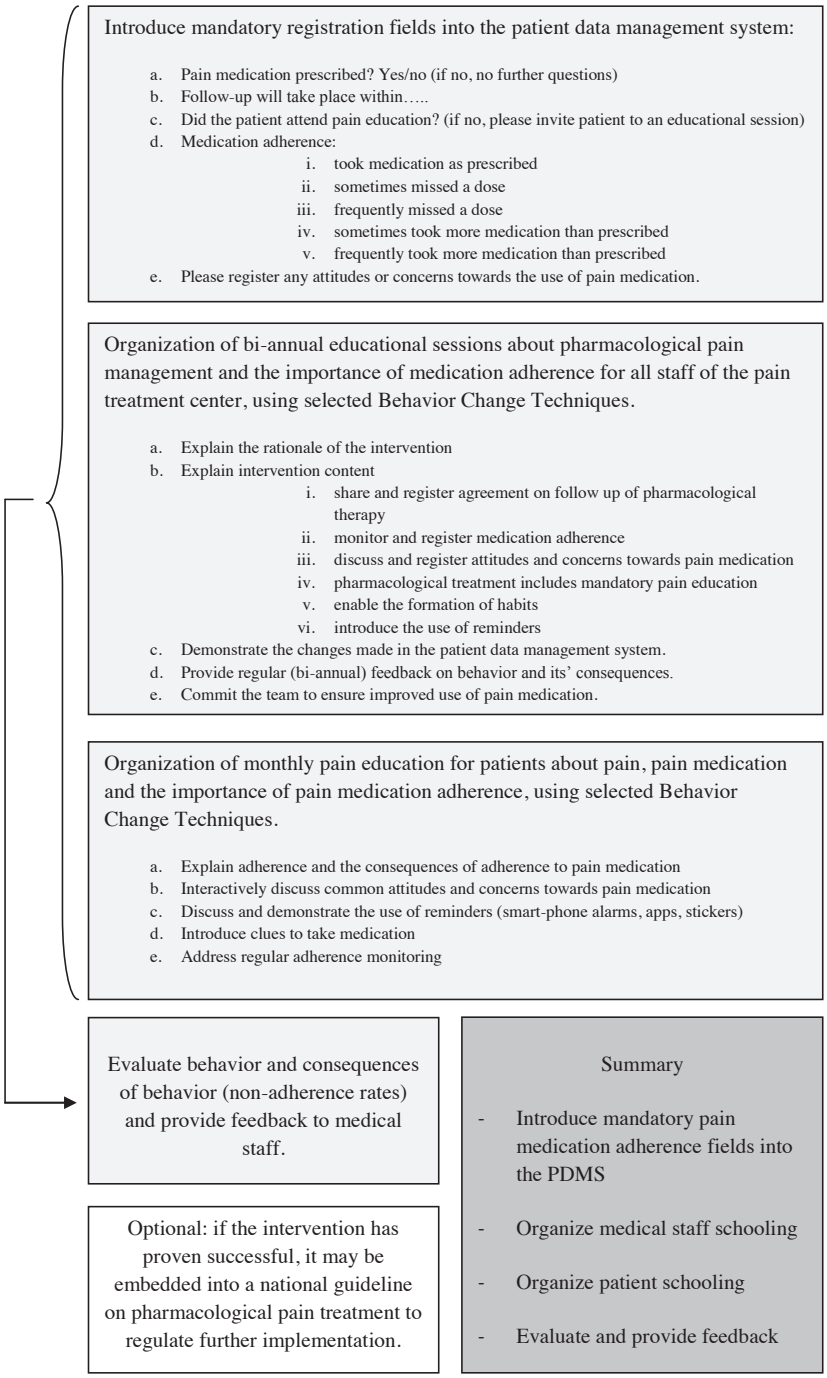

Figure 4. Flow-chart of a COM-B theory-based intervention in a pain treatment center to improve pain medication adherence.

Many medication-adherence interventions have been focusing on the patient, in this analysis however, most behavior changes have to be made by the healthcare providers. Proposed interventions focus largely on the health-care system. First, education of health care providers increases motivation and capability to perform the target behaviors by changing routines of medical prescription and follow-up strategies. Second, optimizing patient data management systems to increase the opportunity and motivation of caregivers to perform target behaviors, such as routine adherence monitoring, which has been shown effective in chronic pain patients.[14] Finally, actual opportunity depends on time available to perform the required behaviors and possibilities to organize patient educational sessions routinely.

Interventions to change patient behaviors also include patient tailored education, which should increase their capability as well as motivation to adhere to a prescription. However, patient motivation depends on more that knowledge alone. For example, intrinsic desires to self-management of health and active coping strategies, which are actually positive qualities of chronic pain patients, have been negatively associated with adherence. Nevertheless, adequate knowledge ensures that patients can make their own decisions regarding their treatment. Finally, introducing reminders to increase automatic motivation and capability has shown to be effective in increasing medication adherence.[17]

The intervention proposal will be evaluated in a clinical trial, in which pre- and post-implementation data will be compared regarding predefined endpoints. Primary endpoint will be medication adherence according to self-report, secondary endpoints will include pain intensity and patient satisfaction. Furthermore, quantification of the impact of introduced changes on healthcare costs have to be made. The adherence intervention, which includes education and an intensified follow-up strategy, will cost time and result in increased treatment costs. At the same time, the intervention may result in savings due to improved treatment effect, timely cessation of unnecessary or ineffective medication and reduction of morbidity caused by non-adherence.

A limitation of this study is that only four clinicians took part in a crucial step of this process: the selection of target behaviors to improve medication adherence. As the determinants of adherence in this population were systematically reviewed earlier, we chose to convert these into target behaviors with a limited team of pain physicians. Furthermore, although patient factors are frequently associated with medication adherence, we did not invite patients to participate in the selection process. Although the interventions account for some well-known patient factors, their contribution might have led to other insights. Finally, the final intervention has not been tested for its impact in daily practice. Although the practical implementation consists of small changes in the data management systems and the introduction of educational sessions, the acceptability in terms of the recipients and those delivering the intervention is not accounted for. In our opinion, the intervention is comprehensive enough to actually work, and practicable enough to be used in clinical practice.

We propose an adherence improving intervention that implies changes into the daily practice of pain medication prescription. Although large changes are generally unwanted in clinical practice, current prescription practices are often insufficient to warrant adequate adherence, which might cause sub-optimal treatment effect, healthcare costs and morbidity. The prescription of chronic pain medication should not be seen as *the* pain therapy but as a part of a treatment regimen including adequate follow-up, adherence monitoring and education during the course of the treatment. If shown to be effective, medication policies might be regulated by introducing prescription guidelines. This might improve medication adherence and reduce unnecessary pain medication taking.

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SUPPLEMENTAL MATERIAL

Table S1. Selection of target behaviors to improve pain medication adherence. Selected target behaviors are presented in bold.

Potential target behaviors relevant to improve pain medication adherence	Impact of behavior change	Likelihood of changing behavior	Spillover score	Measurement score
Avoid high dosing frequency	Promising	Unpromising but worth considering	Unpromising but worth considering	Promising
Avoid polymedication	Promising	Unacceptable	Unpromising but worth considering	Promising
Rethink prescribing pain medication in psychiatric patients	Promising	Unpromising but worth considering	Unpromising but worth considering	Unpromising but worth considering
Rethink prescribing pain medication in patients with a history of drug abuse	Promising	Unpromising but worth considering	Unpromising but worth considering	Unpromising but worth considering
Shared decision making	Promising	Unpromising but worth considering	Promising	Unpromising but worth considering
Define goal and time frame to reach goal	Promising	Unpromising but worth considering	Promising	Unpromising but worth considering
Share agreement on follow up policy	**Very promising**	**Very promising**	**Promising**	**Promising**
Monitor medication adherence	**Very promising**	**Promising**	**Promising**	**Promising**
Educate patients	**Promising**	**Very promising**	**Very promising**	**Very promising**
Discuss attitudes and concerns towards pain medication	**Very promising**	**Very promising**	**Very promising**	**Promising**
Habit formation	**Very promising**	**Very promising**	**Promising**	**Unpromising but worth considering**
Use reminders to use medication	**Very promising**	**Promising**	**Promising**	**Promising**
Self-monitoring of medication adherence	Promising	Unpromising but worth considering	Promising	Very promising

CHAPTER 8

General discussion

The aim of this thesis was to study medication adherence behaviour in chronic non-malignant pain patients to gain insight into its prevalence, factors contributing to adherence and potential interventions to optimize adherence behaviour.

First, we performed a systematic review of the available literature to assess the prevalence and determinants of medication adherence in chronic pain patients. In a prospective correlational study, we analysed the association between patient knowledge of their prescribed pain therapy and medication adherence. Following this study, we performed a randomized clinical trial examine if medication-specific educational intervention was able to increase patient knowledge and improve medication adherence. A second randomized clinical trial was performed to study the effect of three follow-up strategies on medication adherence and pain treatment satisfaction. In this latter study, we additionally focused on the associations between patients' medication-related beliefs, and their medication adherence and pain treatment satisfaction. Finally, using available empirical evidence, a psychological model of behaviour change was applied in order to design a theory-based intervention to improve medication adherence in chronic non-malignant pain patients.

This chapter comments on the main findings of our work in relation to existing evidence and addresses some methodological challenges. The chapter closes by presenting some implications for daily practice and ideas for future research.

Medication adherence

The prevalence of medication non-adherence in chronic non-malignant pain is high: approximately 40 percent of patients does not adhere to prescribed therapy (*chapter 2*). In our studies, adherence rates ranged from 46 to 80 percent. This wide range is a reflection of one of the difficulties in interpreting and comparing adherence research: there is no uniform way to operationalize adherence. In *chapter 3*, any deviation from prescribed therapy on the previous day was considered non-adherent behaviour. In *chapter 4*, we decided to use a different, more realistic, definition to allow patients to miss a dose up to once a week over a larger time frame te be considered adherent. However, to increase reliability, we did combine it with a an additional screening tool to detect non-adherent behaviour. In *chapter 5*, the additional screening tool was left for practical reasons, which was thought to be acceptable because its results were shown to be strongly related to the other measure of adherence .

Medication adherence is complex behaviour, as it:

- can be measured in various ways, using objective (e.g. urine analysis) or subjective (self-report) methods.[1,2]
- can be defined in several ways (e.g. at least 80 percent of medication taken correctly)
- may change in time
- is dependent on several patient, provider and health system factors.[3]

Although medication adherence is mostly presented dichotomously, additional gradations might be appropriate for a more detailed description of this behaviour.[3]

Adherence rates in chronic pain patients were comparable to other chronic illnesses.[3-5] Although chronic pain is a symptomatic disease, presence of pain symptoms do not result in higher adherence rates compared to an asymptomatic disease as hypertension. The necessity and concerns framework provides a solid explanation for poor adherence to pain medication.[6] As chronic pain is a not life-threatening condition, patients may perceive their pain therapy as less important than other chronic therapies. Furthermore, pain medication is frequently associated with side-effects or symptoms of dependence, and patient may perceive the benefit-risk ratio as unsatisfactory.

Underuse of pain medication is more common than overuse.[4,7] Medication overuse always has been an important concern in patients using pain medication and more specifically opioid medication, due to the risk of abuse, addiction and severe adverse events . However, although we found an association between opioid use and overuse, underuse is still more common in patients receiving opioid therapy.[7]

Determinants of pain medication adherence

Patients may be non-adherent due to different beliefs, barriers and a range of other factors (*chapter 2*). Patients may intentionally decide not to take their medicines based on well-informed or mistaken beliefs about the benefits and risks of their medicines. Patients can unintentionally non-adhere to medicines due to forgetfulness, carelessness, health literacy and socioeconomic factors.

Attitudes and concerns towards pain medication were found to be associated with certain patterns of adherence in *chapter 6*. These findings confirm earlier reports about the associations between medication-related beliefs and medication adherence in both chronic conditions in general as well as chronic pain specifically.[6,8-10] Whereas the beliefs about Medicines Questionnaire (BMQ) has frequently been used to measure necessity beliefs and concerns in other chronic conditions [11,12], the Pain Medication Attitudes Questionnaire (PMAQ) is specifically designed for chronic pain management.[9] Perceived need was positively associated with overuse. Concerns about side effects were positively associated with underuse non-adherence (*chapter 6*). The relation between patient beliefs about pain medication and their actual patterns of medication use might be of use in clinical practice. Addressing beliefs and concerns about medicines during patient counselling might identify patients at risk for non-adherence to medications. Although the original 47-item PMAQ might be unsuited for use in daily practice, the revised 14-item PMAQ may be acceptable for routine use.[13] In patients with low necessity beliefs or high level of concerns about prescribed therapy, the risk of non-adherence is considerable. In these patients, an informed and shared-decision regarding proposed therapy or alternative treatment might be considered to optimize treatment adherence and patient satisfaction.

We found an association between knowledge of prescribed pain medication and adherence to this medication (*chapter 3*). This association confirmed earlier findings, but was not confirmed in the next trial, possibly due to methodological differences between both studies. Whereas patient education have been shown to improve medication adherence [14,15], our educational intervention did not (*chapter 4*). Our intervention was relatively simple and consisted of a single standardized video. Successful educational interventions were described to be more comprehensive and patient tailored.[4] To be successful, educational interventions should not only be able to improve knowledge, but also increase motivation through assessment of existing beliefs about prescribed therapy.

A good relationship between patient and physician substantially improves adherence.[3] Centralizing patient priorities, and addressing cultural belief and attitudes are important to reach a shared-decision regarding therapy.[16] As time constraints limit the possibility to discuss patient beliefs about medications [17], we hypothesized that increasing follow-up frequency might lead to better medication adherence and treatment satisfaction. However, our study results did not support these thoughts (*chapter 5*). One of the reasons might be that the actual contents of the additional contacts were not controlled. If medication adherence and beliefs about pain medications were systematically addressed during each of the extra sessions, the results might have been different.

Medication adherence and treatment outcome

Medication adherence has been shown to have a significant effect on therapy outcome and health care costs in chronic illnesses.[18] In chronic pain, however, this relationship is less clear. Some studies demonstrate an association between pain medication and treatment outcome [19,20], other do not.[10,21,22] There are some explanations that are partly methodological and partly due to the nature of chronic pain. Therapy outcome is mostly reported by means of pain intensity levels. Pain intensity has been associated with adherence in both directions (*chapter 2*). If there is little or no pain, patients may feel pain medication unnecessary. High pain levels may be interpreted as a higher need for pain medication, and may therefore lead to better adherence or even overuse of pain medication. On the other hand, patients who do not use their medications may have higher pain intensities than patients that use their prescription correctly. This explains the variety of relationships reported between pain intensity and treatment outcome in *chapter 2*. We did not find a relationship between medication adherence and pain intensities in our studies. In our last trial, we intentionally defined treatment outcome differently by using the Pain Treatment Satisfaction Scale. The fact that we still did not find a relationship between adherence and outcome might be caused by the low number of patients that were actually non-adherent in this study.

The question rises if it is important to pursue adherent behaviour in chronic pain by means of adherence-improving interventions when a causal relationship between medication adherence and outcome has not been found. However, besides the reasonable assumption

that some adherence is necessary for medication to work, non-adherence leads to an inability to accurately assess the effect of prescribed therapy, and might lead to unnecessary visits or therapy changes. Furthermore, incorrect pain medication use, especially overuse, might lead to health risks.

Interventions

The high levels of non-adherence in chronic illnesses indicate a definite need to intervene. Successful interventions have been shown to be complex and multifactorial, and often difficult to implement in clinical practice. However, our studies demonstrate that limited interventions, using small parts of effective complex interventions, were unsuccessful, as were other studies in chronic non-malignant pain patients.[23] In the last chapter, we used a theoretical framework and available evidence on pain medication adherence to design an intervention that is comprehensive enough to be effective, targeting multiple factors affecting adherence, without unacceptable changes that couldn't be applied in clinical practice. The most important conclusion of this approach was that the key focus of the intervention should be the health care provider, instead of the patient. The finding that providers spend less than a minute to discuss all aspects of new prescription medications, indicates that there might be a need for restructuring prescribing practices.[17] The health care team should be committed to bring pharmacological pain management to a higher level, implementing the possible steps described in *chapter 7*.

Implications for future research and clinical practice

In chronic pain management the prevalence and determinants of medication non-adherence are well-investigated. However, although validated measures of medication adherence exist, it would be helpful to reach consensus about how to define and validly measure adherence in the chronic pain population. Furthermore, a prospective study using validated measures of pain treatment outcome, might further elucidate the relationship between medication adherence and outcome. Finally, new adherence-improving interventions have to be designed and studied for its effect on medication use.

In conclusion, the magnitude of the problem of non-adherence in chronic non-malignant pain patients is high. Therefore, it deserves appropriate attention from all stakeholders involved. Although medication adherence concerns patients' behaviours, the health care providers carry an important responsibility to provide optimal conditions for patients to adhere to their recommendations. The findings in this thesis demonstrate that proper patient selection for pharmacological pain therapy should include a basic risk factor screening for non-adherence and an open discussion about the views of patients about the proposed therapy. An optimal strategy for ensuring adequate adherence has not been found, and might not exist for a large group of patients. However, each individual prescription of chronic pharmacological pain therapy should include efforts to promote optimal medication adherence.

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CHAPTER 9

Summary
Nederlandse samenvatting

SUMMARY

In **chapter 1**, the rationale for this thesis is described. Chronic pain is a common chronic condition which is frequently treated with the prescription of pain medication. Non-adherence to prescribed medication is common and may account for sub-optimal treatment results. Although many reports have described determinants of medication adherence in chronic pain patients, these have not been translated into successful interventions to improve it. The aim of the work presented in this thesis was to explore the concept of medication adherence in chronic non-malignant pain patients in order to design effective interventions to improve the use of prescribed pain therapy.

Chapter 2 describes the results of a systematic review of the prevalence and determinants of medication non-adherence in chronic pain patients. In the twenty-five studies reviewed, a mean of forty percent did not use their medication as prescribed. Underuse of medication was more common than overuse. Factors associated with non-adherence in general, and underuse and overuse specifically, are presented. To improve medication adherence, these risk factors should be taken into account when prescribing pharmacological pain therapy.

In **chapter 3**, the results of a prospective observational study of the association between knowledge and adherence to a pharmacological prescription in patients with chronic non-malignant pain are presented. Basic knowledge of pain medication was found to be low and did not improve during the course of the study. Knowledge of the prescription was found to be associated with adherence to this prescription.

Following this study, we designed an educational intervention aimed at improving medication adherence. The effect of this intervention was investigated in a randomized clinical trial described in **chapter 4**. Although standardized information about prescribed therapy did increase knowledge about this therapy, it did not change medication adherence or treatment outcome parameters.

We hypothesized that an increased number of contacts during follow-up of pharmacological therapy would improve medication adherence. **Chapter 5** describes the results of a randomized controlled trial to compare the effect of three different follow-up strategies on medication adherence, therapy outcome and health care consumption in chronic non-malignant pain patients: (1) standard care, (2) intensive hospital-initiated follow-up, in which patients were contacted every two weeks, and (3) intensive patient-initiated follow-up, in which patients received standard care and additional follow-up on demand. No differences were found in medication adherence. Patient initiated care did not lead to increased number of unplanned contacts. Although patient satisfaction regarding the provision of information was higher in both the intensive hospital- and patient initiated follow-up groups, other outcomes did not differ.

In **Chapter 6**, a prospective investigation of the relation between patients' beliefs about pain medication and their medication adherence and treatment outcome is presented. Concerns

over side effects at baseline were positively associated with underuse after 11 weeks. Perceived need was positively associated with overuse. Concerns over side effects and mistrust in the doctor at baseline were negatively associated with patient satisfaction regarding prescribed medication after 11 weeks, and concerns over side effects and concerns over withdrawal were positively associated with presence of side effects after 11 weeks. This chapter discusses the importance of taking patients' beliefs about medication into account when prescribing pain medication.

Chapter 7 describes the use of a theoretical psychological model of behaviour change in order to design an intervention to improve medication adherence in chronic pain patients. An important finding is that most interventions should be focused on providers of pain therapy. The proposed intervention consist of three elements: (1) changes in the patient data management systems to facilitate adherence monitoring, (2) repeated education of medical staff to commit the team to the proposed intervention and (3) routine and mandatory education of chronic pain patients following prescription of pain medication.

In the general discussion in **chapter 8**, the main findings of this thesis are discussed. It presents recommendations for future studies of pain medication adherence in chronic pain patients. It re-emphasises the importance of screening for risk factors of non-adherence when prescribing pharmacological pain therapy. The chapter concludes with the statement that, although an optimal strategy for ensuring adequate adherence has not been found, and might not exist for a large group of patients, each individual prescription of chronic pharmacological pain therapy should include efforts to promote optimal medication adherence.

NEDERLANDSE SAMENVATTING

In de introductie in **hoofdstuk 1** worden de achtergronden bij dit proefschrift beschreven. Chronische pijn is een veel voorkomende chronische ziekte. De behandeling bestaat vaak uit het voorschrijven van pijnmedicatie. Gebrek aan therapietrouw komt vaak voor en kan een verklaring zijn voor de gebrekkige resultaten van de behandeling. Ondanks dat er veel determinanten beschreven zijn van medicatietrouw van patiënten met chronische pijn, zijn deze nog niet vertaald in effectieve interventies on deze trouw te verbeteren. Het doel van het onderzoek beschreven in dit proefschrift was om een beter inzicht te krijgen in de therapietrouw van patiënten met chronische benigne pijn om zo effectieve interventies te ontwerpen om het gebruik van pijnmedicatie te verbeteren.

In **hoofdstuk 2** worden de resultaten beschreven van een systematische review van studies naar de prevalentie en determinanten van medicatie-ontrouw bij patiënten met chronische pijn. In de 25 geselecteerde studies gebruikte gemiddeld 40 procent van de patiënten de medicatie niet zoals voorgeschreven. Ondergebruik van pijnmedicatie kwam vaker voor dan overgebruik . Factoren die geassocieerd zijn met medicatietrouw in het algemeen, of die specifiek met ondergebruik of overgebruik gerelateerd zijn, worden in dit hoofdstuk beschreven. Om medicatietrouw te verbeteren is het goed dat men rekening houdt met deze factoren bij het voorschrijven van een medicamenteuze pijnbehandeling.

In **hoofdstuk 3** worden de resultaten van een prospectieve observationele studie naar de relatie tussen kennis van - en trouw aan een voorschrift voor pijnmedicatie uiteengezet. Basale kennis van pijnmedicatie was laag en nam niet toe gedurende de looptijd van de studie. Kennis van het specifieke voorschrift was geassocieerd met trouw aan dit voorschrift.

Na deze studie werd in een gerandomiseerde gecontroleerde studie onderzocht of gestandaardiseerde educatie over het specifieke voorschrift de trouw aan dit voorschrift zou verbeteren. De resultaten worden beschreven in **hoofdstuk 4**. Ondanks dat de educatieve interventie over het voorgeschreven pijnmedicijn de kennis van het voorschrift verbeterde, trad geen verandering op in medicatietrouw of uitkomst van de behandeling.

Onze hypothese was dat een toename van het aantal patiëntcontacten gedurende de follow-up van farmacologische pijnbehandeling de therapietrouw zou verbeteren. In **hoofdstuk 5** worden de resultaten van een gerandomiseerde gecontroleerde studie beschreven waarin het effect van drie verschillende follow-up strategieën worden vergeleken op medicatietrouw: (1) standaard zorg, (2) intensieve ziekenhuis-geïnitieerde follow-up, waarbij patiënten elke twee weken werden opgevolgd, en (3) intensieve patiënt-geïnitieerde follow-up, waarbij patiënten naast standaard zorg op ieder moment aanvullende aandacht konden krijgen. Er werd geen verschil in medicatietrouw gevonden tussen de drie groepen. Patiënt-geïnitieerde follow-up leidde niet tot meer ongeplande contacten. Ondanks dat de tevredenheid van patiënten over de informatieverschaffing hoger was in zowel de intensieve ziekenhuis- als patiënt-geïnitieerde follow-up groep, waren overige tevredenheidsscores niet verschillend.

In **hoofdstuk 6** worden de resultaten van een prospectief onderzoek naar de relatie tussen gedachtes van patiënten over pijnmedicatie, hun medicatietrouw en behandeluitkomsten besproken. Angst voor mogelijke bijwerkingen voorafgaand aan de behandeling was positief geassocieerd met ondergebruik van pijnmedicatie na 11 weken. Een ervaren behoefte aan pijnmedicatie was positief geassocieerd met overgebruik. Angst voor bijwerkingen en gebrek aan vertrouwen in de behandelaar voorafgaand aan de behandeling waren negatief geassocieerd met tevredenheid over het voorgeschreven medicijn na 11 weken. Angst voor bijwerkingen en angst voor onttrekkingsverschijnselen waren positief geassocieerd met het daadwerkelijk optreden van bijwerkingen na 11 weken. Dit hoofdstuk onderstreept dat het van belang is rekening te houden met de gedachtes van de patiënt over pijnmedicatie als gekozen wordt voor een medicamenteuze pijnbehandeling.

In **hoofdstuk 7** wordt beschreven hoe een theoretisch model van gedragsverandering gebruikt wordt om een interventie te ontwerpen die medicatietrouw van patiënten met chronische pijn kan verbeteren. Een belangrijke constatering is dat interventies vooral op de zorgverlener gericht moeten zijn. De voorgestelde interventie bestaat uit drie onderdelen: (1) veranderingen in het elektronische patiëntendossier die monitoring van medicatietrouw ondersteunen, (2) herhaalde scholing van zorgverleners voor maximale en eensgezinde betrokkenheid bij de voorgestelde interventie en (3) routinematige en verplichte scholing voor patiënten met chronische pijn nadat gestart is met medicamenteuze pijnbehandeling.

In **hoofdstuk 8** wordt nader ingegaan op de belangrijkste bevindingen uit dit proefschrift. Er worden aanbevelingen gegeven voor toekomstige studies op het gebied van medicatietrouw bij patiënten met chronische pijn. Opnieuw wordt benadrukt dat het belangrijk is om een inschatting te maken van het risico op medicatie-ontrouw als nieuwe medicatie wordt voorgeschreven. Het hoofdstuk eindigt met de stellingname dat, ondanks dat een optimale strategie om medicatietrouw te bevorderen niet werd gevonden, en mogelijk niet bestaat voor deze patiëntengroep als geheel, ieder individueel voorschrift van pijnmedicatie gepaard zou moeten gaan met inspanningen om optimale therapietrouw te bevorderen.

APPENDICES

Dankwoord
Curriculum Vitae
PhD portfolio
Publications

DANKWOORD

In de afgelopen jaren hebben veel mensen bijgedragen aan de totstandkoming van dit proefschrift. Ik wil alle collega's, vrienden en familie danken hiervoor. Jullie hulp bij het onderzoek, de motiverende of relativerende gesprekken en jullie gezelschap waren en zijn belangrijk voor me. Enkele mensen wil ik graag ik het bijzonder bedanken.

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CURRICULUM VITAE

Leon Timmerman werd geboren op 29 oktober 1975 te Rotterdam. Hij behaalde zijn gymnasium-diploma aan het Caland Lyceum te Rotterdam. In 1994 is hij begonnen aan de studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Het doctoraalexamen werd behaald in 1998 en het artsexamen werd afgerond in april 2001.

Na het afronden van zijn geneeskunde opleiding heeft hij van 2001 tot 2003 twee jaar ervaring opgedaan als assistent geneeskundige niet in opleiding (AGNIO) op de afdelingen interne geneeskunde, longziekten en cardiologie van het Zuiderziekenhuis in Rotterdam. In 2003 startte hij met de opleiding tot anesthesioloog in het Sint Antonius Ziekenhuis in Nieuwegein (opleider: Dr. H.P.A. van Dongen). In het laatste jaar van de opleiding richtte hij zich op het aandachtsgebied pijngeneeskunde. Na afronding van de opleiding werkte hij van april 2008 tot en met december 2009 in het Medisch Centrum Haaglanden in Den Haag als anesthesioloog-pijnspecialist. Sinds januari 2010 is hij werkzaam als anesthesioloog-pijnspecialist in het Sint Antonius Ziekenhuis in Nieuwegein.

Sinds 2010 is hij geregistreerd in het aandachtsgebied Pijngeneeskunde. In 2011 werd gestart met het onderzoek dat tot dit proefschrift heeft geleid.

Leon woont samen met Suzanne en hun kinderen Julia en Stefan in Zeist.

PHD PORTFOLIO

Name PhD student: Leon Timmerman
St. Antonius Hospital
Department of Anesthesiology,
Intensive Care and Pain Medicine

PhD period: 2011-2017
Promotor: Prof. dr. F.J.P.M. Huygen
Co-promotor: Dr. D.L. Stronks

1. PhD training

Courses

BROK- course	2016
SPSS and Medical Statistics basic course	2012

Conferences

Annual congress on pain, Den Bosch	2016
Annual congress on pain, Utrecht	2015
Annual congress on pain, Brugge	2013
Third biannual international pain congress, Middelburg	2012
7th congress of the European Federation of IASP chapters, Hamburg	2011
Masterclass neuropathic pain, Rotterdam	2011

2. Teaching

Bi-monthly education for chronic pain patients: 'Chronic pain and pain treatment'.

Presentation for the Dutch Society of Occupational Experts 2016: 'Pain and Work'.

Regional course residents anesthesiology 2016: 'Pharmacological pain management and medication adherence'.

Regional course residents anesthesiology 2014: 'Low back pain in the elderly patient'.

Regional course residents anesthesiology 2012: 'Awareness and monitoring of anesthetic depth'.

Post-graduate course pharmacology 2011: 'Pain management at the Emergency Department'.

Course General Practitioners 'duodagen' 2011: 'Advanced pain management'

Regional course residents anesthesiology 2010: 'Inhalational anesthetics'

3. Abstracts and presentations

Ramsodit P, Timmerman L. The Effect of Clonidine As An Additive to Local Anaesthetics On the Duration of Postoperative Analgesia After Orthopaedic Foot Surgery: A Randomized Clinical Trial. P. Anesth Analg 2016; 123(3S_Suppl 2): 647-48.

L. Timmerman, DL Stronks, JG Groeneweg, FJPM Huygen. Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review. Annual scientific meeting Dutch Society of Anesthesiology 2016, Rotterdam.

L. Timmerman, DL Stronks, JG Groeneweg, FJPM Huygen. Medication adherence and treatment outcome in patients with chronic pain. Scientific meeting department of Anesthesiology, Erasmus MC Rotterdam.

L. Timmerman, DL Stronks, JG Groeneweg, FJPM Huygen. The value of medication-specific DVD-information on medication adherence and treatment outcome in patients with chronic pain: a randomized clinical trial. Annual scientific meeting Dutch Society of Anesthesiology 2014, Zeist.

Brackel AML, Marting LN, Timmerman L. Comparison of local infiltration analgesia with epidural analgesia after total knee arthroplasty: a randomized clinical trial (NCT01489631). Annual scientific meeting Dutch Society of Anesthesiology 2014, Zeist.

L. Timmerman, R Stellema, DL Stronks, JG Groeneweg, FJPM Huygen Adherence to pharmacological pain therapy in patients with non-malignant pain: the role of patients' knowledge of pain medication. Annual scientific meeting Dutch Society of Anesthesiology 2013, Zeist.

Articaine and lidocaine for spinal anesthesia in day-case surgery.L Timmerman, EP van Dongen, E Tromp, EJM Andriessen, CAJ Knibbe. XXIV Congress of the European Society of Regional Anaesthesia and Pain Therapy, Valencia 2007 en 7th International Congress on Ambulatory Surgery, Amsterdam 2007.

Perifere zenuwstimulatie voor pijn na traumatisch zenuwletsel.
L Timmerman, AL Liem.
Voorjaarsvergadering Nederlandse Vereniging voor Plastische Chirurgie, Utrecht 2007.

Peripheral nerve stimulation for intractable pain.
L Timmerman, AL Liem.
World Institute of Pain congress 2004, Barcelona.

4. Studies

2011-2013: STRIDE study: A Multicentre, Single-Arm, Open-Label Study of the Repeated Administration of QUTENZA™ for the Treatment of Peripheral Neuropathic Pain. Principal Investigator.

2012-2014: PAINTHER study: The value of medication-specific DVD-information on medication adherence and treatment outcome in patients with chronic pain: a randomized clinical trial. Principal Investigator.

2013-2014: ANALGESIETKP: Comparison of intra-articular infiltration and gabapentine with epidural analgesia after total knee replacement surgery: a randomized clinical trial". Principal Investigator.

2014-2016: PANTHER II study: The effect of hospital-initiated and patient-initiated intensive follow-up on medication adherence in patients with chronic pain: a randomized controlled clinical trial. Principal Investigator.

2015-2017: CALPAFAS: The effect of clonidine as additive to local anaesthetics on duration of postoperative analgesia after orthopaedic foot surgery: a randomized clinical trial. Investigator.

2016 - present: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BIIB074 in Subjects With Neuropathic Pain From Lumbosacral Radiculopathy. Principal Investigator.

2017-present: EFIC PAIN OUT project: Optimizing management of perioperative pain in Europe. Principal Investigator.

5. Other

2015 Winnaar 'St Antonius uitkomstprijs' voor reductie postoperatieve pijn, uitgereikt tijdens symposium 'Uitkomsten van onze Zorg'.

PUBLICATIONS

Papers related to this thesis

Timmerman L, Stronks DL, Groeneweg JG, Huygen FJPM. The value of medication-specific education on medication adherence and treatment outcome in patients with chronic pain: a randomized clinical trial. Pain Med. 2016 Oct;17:1829-1837.

Timmerman L, Stronks DL, Groeneweg JG, Huygen FJPM. Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review. Acta Anaesthesiol Scand 2016; 60(4): 416-31.

Timmerman L, Stellema R, Stronks DL, Groeneweg JG, Huygen FJPM. Adherence to pharmacological pain therapy in patients with non-malignant pain: the role of patients' knowledge. Pain Pract 2014; 14: 701-8.

Timmerman L, Stronks DL, Huygen FJPM. The design of a theory-based intervention to improve medication adherence in chronic pain patients. Curr Med Res Opin. 2017;33:1293-1301.

Timmerman L, Stronks DL, Groeneweg JG, Huygen FJPM. Comparison of the effect of intensified hospital-initiated follow-up, patient-initiated follow-up and standard care on medication adherence in patients with chronic pain: a randomized controlled clinical trial. Submitted

Timmerman L, Stronks DL, Groeneweg JG, Huygen FJPM. The relation between patients' attitudes towards pain medication and their medication adherence and treatment outcome in chronic pain patients: a prospective study. Submitted

Papers not related to this thesis

Timmerman L, Megens HAM. Detecting intravascular injection during caudal anesthesia in children. Eur J Anaesthesiol 2007; 24(10): 1060-2.

Brackel AML, Timmerman L. Anesthesie bij plaatsing van een Totale Knieprothese. Anesthesiologie en Intensive Care 2014 (3): 21-25.

Liem AL, Timmerman L. A new approach to neurostimulation for peripheral pain.

Puesta al dia en anestesia regional y tratamiento del dolor 2006; 9:235-237.

Steketee K, Timmerman L, Ziel-van der Made AC, Doesburg P, Brinkmann AO, Trapman J. Broadened ligand receptor responsiveness of androgen receptor mutants obtained by random

amino acid substitution of H874 and mutation hot spot T877 in prostate cancer. Int J Cancer 2002; 20;100:309-17.

Book chapters

Timmerman L, Huygen FJPM. Chronische medicamenteuze pijnbehandeling. In: P.J. Hennis, H.P.A. van Dongen, W.A. van Klei. Leerboek anesthesiologie. Houten: Uitgeverij Bohn Stafleu van Loghum 2013. Hoofdstuk 47.

Timmerman L. Hart en circulatie. In: P.G. Noordzij, M. Klimek en J.J. Landman. Klinische anesthesiologie. Utrecht: Uitgeverij de Tijdstroom 2017. Hoofdstuk 5.