

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

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Conflicts of Interest

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Background: Chronic pain is commonly treated with analgesic medication. Non-adherence to prescribed pain medication is very common and may result in sub-optimal treatment outcome. The aim of this review was 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% with a weighted mean of 40%. 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 use 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.

Editorial comment: what this article tells us

This review analyzes and presents the published evidence concerning chronic pain patient non-adherence to their treatment programs with focus on medications – a challenging phenomenon to study.

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 multi-disciplinary approach, pharmacological therapy remains a cornerstone of chronic pain treatment. Although 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 was 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 pre-defined 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 were 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 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 four out of five of the essential questions were answered with 'yes' and if the total score was 7 or higher.

Results

The reviewing process is presented in Fig. 1. The Pubmed and Embase search retrieved 2803 and

Table 1 Quality assessment checklist for observational adherence studies constructed by Pasma et al.

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, MEMES, pharmacy records and a validated questionnaire are considered valid, patient questionnaire and/or interviews and health care 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)

Bold items indicate the 'essential criteria'.

3990 citations, respectively. Eighty full-text articles were retrieved, 25 articles were included in this review^{14,19–42}. Excluded articles are listed in Supporting Information Appendix 1. Most articles were excluded because they focused on opioid abuse. The design and method of adherence measurement of the included studies are shown 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

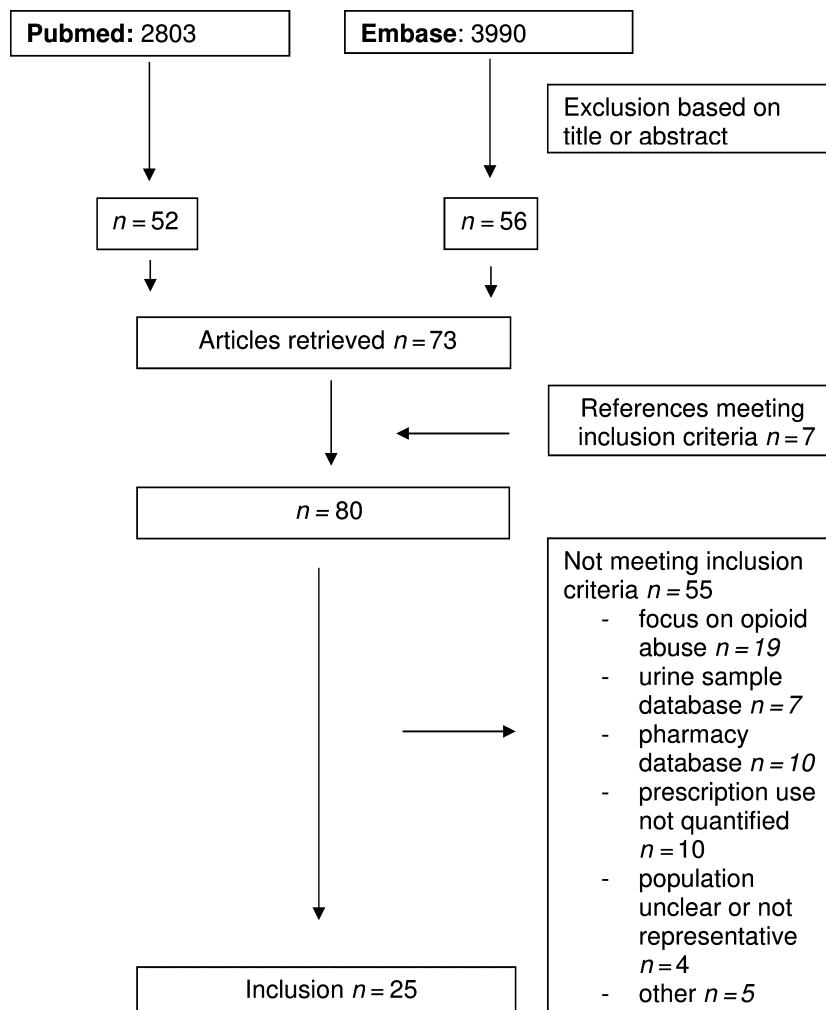


Fig. 1. Flow chart of study selection.

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 selective serotonin re-uptake inhibitors (SSRIs) or gabapentin treatment²⁹ (Table 3).

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

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

MMAS, Morisky Medication Adherence Scale (4- or 8-item scale); MEMS, Medication Event Monitoring System; SSRI, Selective Serotonin Reuptake Inhibitor.

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.^{32,33} 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

3. Condition-related factors

Pain intensity was positively associated with adherence.^{27,29,33} More specifically, underuse

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

Author	Year	Population	Non-adherence (%)			Definition	Comments
			G	U	O		
Packard ¹⁹	1986	Headache	52			Non-adherence: Not taking medication as prescribed, alcoholism or drug abuse.	Non-adherence at second follow-up visit: 38.6%
Weinberge ²⁰	1991	Osteoarthritis		33		Non-adherence: report of missing a single dose or more.	33.4% follow-up 11 months
Berndt ²¹	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 ²⁷	2006	Chronic non-malignant pain	37			Non-adherence: medication taken less often, more often, or at a different dose.	
Lewis ¹⁴	2010	CNPC 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 ³¹	2010	Chronic non-malignant pain	48	32	14	Non-adherence: any deviation from prescription	Underuse 32%; overuse 14%, both 2%
Broekmans ³²	2010	Chronic non-malignant pain	62	40	14	Non-adherence: any deviation from prescription	Underuse 40%; overuse 14%; both 8%
Stern ³⁴	2011	Chronic non-malignant pain		34		Adherence: not having missed a single dose in the previous week.	According to physician: 19.6%
Grattan ³⁸	2012	Chronic opioid use, no history substance abuse		51		Overuse: Taking more than the dosage allowed Misuse: opioid use for other than pain symptoms. Aberrant behavior: giving opioids to or getting them from others.	Underuse not reported Overuse: 51% Misuse: 43% Aberrant behavior: 17%
Timmerman ³⁹	2013	Chronic non-malignant pain	58			Non-adherence: any deviation from the prescribed therapy the day before adherence measurement.	
Markotic ⁴⁰	2013	Chronic non-malignant pain	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

Table 3 (Continued)

Author	Year	Population	Non-adherence (%)			Definition	Comments
			G	U	O		
Sewitch ²⁴	2004	in patients aged > 65 Fibromyalgia		47		Non-adherence: one positive answer on MMAS-4.	adherence, 41% low adherence
Dobkin ²⁸	2006	Fibromyalgia		53		Non-adherence: one positive answer on MMAS-4.	
Chang ³⁵	2011	Chronic non-malignant pain in older adults, opioids prescribed	57	47	11	Higher scores MMAS-8 indicate better adherence.	Underuse 47%; overuse 10%
Nicklas ³³	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 ³⁶	2011	Chronic non-malignant pain	38	45	27	Four questions, two related to overuse and two related to underuse, were answered on a five-point scale.	Underuse 44.8%; overuse 26.9%
Barth ⁴¹	2014	Chronic non-alcoholic pancreatitis, opioid users.	39			Non-adherence: Current Opioid Misuse Measure (COMM) positive for misuse behavior.	
De Klerk ²²	1996	Ankylosing Spondylitis	22			Adherence: percentage of days on which dose taken as prescribed (MEMS)	MEMS
Mulleners ²³	1998	Migraine	33			Adherence: correct number of openings MEMS	
Giannopoulos ²⁹	2007	Painful diabetic neuropathy	12			Non-adherence: receiving less than 75% of scheduled dosages	9.2% using pill count/56% not on schedule Definition more liberal than other studies
Manchikanti ²⁵	2005	CNCP opioid users	32			UDT negative for prescribed drug	Urine screening Underuse 32%; non-prescribed opioid 7%; illicit drugs 23%
Ives ²⁶	2006	CNCP opioid users	8			UDT negative for prescribed drug	Underuse 7.6%; non-adherence including diversion, prescription forgery and multiple providers 32%

Table 3 (Continued)

Author	Year	Population	Non-adherence (%)			Definition	Comments
			G	U	O		
Navato ³⁰	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%
Bronstein ³⁷	2011	CNCP, opioids prescribed	41			UDT negative for prescribed drug: levels inconsistent with prescribed dosage	Non-adherence: 41% Illicit substance: 5%
Mattellano ⁴²	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%

G, general non-adherence; U, underuse; O, overuse.

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 study⁴⁰ 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 SSRIs 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 association³⁹ 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 toward 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}

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

Author	Year	N	Determinants of non-adherence	Comments
Berndt ²¹	1993	99	Polymedication, history of drug abuse	
Mulleners ²³	1998	29	Higher dosing frequency	Article described medication prophylaxis instead of symptomatic treatment
De Klerk ²²	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 ²⁴	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 ²⁸	2006	121	Lower affective pain ratings, higher psychological distress	
McCracken ²⁷	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 ²⁵	2005	200	Long-acting opioids did not improve adherence	
Ives ²⁶	2006	196	Younger age, drug or DUI conviction, history of cocaine or alcohol abuse	
Grattan ³⁸	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 ⁴¹	2014	307	Depression, high pain intensity, impaired psychological quality of life, alcohol use	
Mattaliano ⁴²	2014	120	Age, pain level, sex, ethnicity, injury compensation did not predict aberrant drug taking behavior	
Giannopoulos ²⁹	2007	93	Patients on SSRIs were more compliant than patients on gabapentin	
Nicklas ³³	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 ³¹	2010	281	Underuse: younger age, more use of (non-prescribed) self-medication Overuse: younger age, higher dose frequency, opioids prescribed, smoking	
Broekmans ³²	2010	265	Underuse: higher number of prescribed analgesics, self-medication, lower pain intensity, active coping, lack of information, side effects	

Table 4 (Continued)

Author	Year	N	Determinants of non-adherence	Comments
Rosser ³⁶	2011	239	Overuse: higher number of prescribed analgesics, smoking Overall: higher number of prescribed analgesics, prescription of non-opioids 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 ³⁴	2011	1351	Higher pain intensity	
Markotic ⁴⁰	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 ³⁹	2013	96	Less knowledge of the prescription, lower age	

Although 17 studies fulfilled 7 out of 11 methodological criteria, four of these studies did not meet four 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: four questions (MMAS-4) or eight questions (MMAS-8).

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, e.g., 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

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
	1	2	3	4	5	6	7	8	9	10	11	
Question												
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.

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 explana-

tion for the wide range of non-adherence rates may be that taking medication is in fact complex behavioral pattern, 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 over 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 monitor-

ing 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. Polymedication 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 toward 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 condi-

tions 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 behavioral 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 toward 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, e.g., 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 data-

bases, 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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Appendix 1. References of excluded articles