Prevalence and Predictors of Patient Nonadherence to Pharmacological Acute Pain Therapy at Home After Day Surgery

ORIGINAL ARTICLE

Prevalence and Predictors of Patient Nonadherence to Pharmacological Acute Pain Therapy at Home After Day Surgery: A Prospective Cohort Study

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■ **Abstract**

Background: Good adherence to prescribed analgesics can be crucial to suppress or even prevent acute postoperative pain after day surgery. The aim of this study was to analyze prevalence and predictors of analgesic nonadherence after day surgery.

Methods: Elective patients scheduled for day surgery were prospectively enrolled from November 2008 to April 2010. Outcome parameters were measured by using questionnaire packages at 2 time points: 1 week preoperatively and 4 days postoperatively. The primary outcome parameter was analgesic nonadherence. Adherence was defined according to the patient's response to the questionnaire item "analgesia use as prescribed": full adherence, "yes"; partial adherence, "yes, sometimes"; nonadherence, "no." Bivariate and multivariate logistic regression analyses were performed to identify predictors of analgesic nonadherence.

Results: A total of 1,248 patients were included. The prevalence rates of analgesic nonadherence and partial adherence were 21.6% and 20.0%, respectively, in the total study population but dropped to 9.4% and 19.8%, respectively, in patients with moderate to severe pain. Low postoperative pain intensity and short duration of surgery were the most important predictors of analgesic nonadherence. The most important preoperative predictors for analgesic nonadherence were low preoperative pain intensity, low preoperative expectations of pain, and low fear of short-term effects of surgery.

Conclusion: Analgesic nonadherence and partial adherence are common after day surgery but decrease as average pain intensity increases. Patients at risk for analgesic nonadherence can be identified during the preoperative period based on preoperative pain intensity, preoperative expectations of pain, and fear of surgery. ■

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INTRODUCTION

Despite increased awareness and improvements in postoperative pain management over the past decades, the prevalence of outpatients suffering moderate to severe acute postoperative pain at home still remains high and varies from 9% to 40%.[1–5]

However, sufficient control of postoperative pain is essential as acute postoperative pain is an important risk factor for the development of chronic postsurgical pain[6–8] and can cause unanticipated hospital admission of outpatients.[9–11]

Obviously, good adherence to prescribed postoperative pain medication can be crucial to suppress or even prevent moderate to severe acute postoperative pain after day surgery. Medication adherence or compliance is defined as "the extent of correspondence between the patient's actual dosing history and the prescribed regimen."[12] Furthermore, the National Institute for Health and Clinical Excellence (NICE) guidelines posit that "adherence presumes an agreement between prescriber and patient about the prescriber's recommendations."[13,14]

There are many causes of nonadherence, but they fall into 2 overlapping categories: intentional and unintentional.[14] Unintentional nonadherence occurs when the patient intends to follow the agreed treatment but is prevented from doing so by barriers that are beyond his or her control. Examples include poor recall or difficulties in understanding the instructions, inability to pay for the treatment, or simply forgetting to take it. Intentional nonadherence occurs when the patient decides not to follow the treatment recommendations.[14] Numerous beliefs and preferences may influence the patient's perceptions of the pharmacological treatment and the motivation to start and continue with it.[14]

Analgesic nonadherence in patients with chronic pain is a frequent problem and a well-studied topic in the literature.[13,15,16] In contrast, analgesic nonadherence in patients with acute pain is not well studied.[17] An explanation for the paucity of information on this topic can be found in the fact that the prescription of analgesics for acute postoperative pain traditionally has been by the pro re nata convention or, in other words, "as needed."[18] Nevertheless, numerous researchers have recommended the use of fixed-dose analgesic administration schedules during the initial 48-hour postoperative phase in order to maintain a steady blood level of the analgesic and keep the patient pain free.[19] Consequently, pre-emptive use of analgesics in the treatment of acute pain has gained importance in the postoperative setting, and the incidence and determinants of patient adherence to these fixed-dose schedules need to be investigated. Identification of those patients at risk for analgesic nonadherence after day surgery may provide new insights for patient counseling, assistance with coping, and selection of future patients that might benefit from a planned overnight stay with the aim of prevention of the development of prolonged severe pain.

Therefore, the objective of our study was to analyze the prevalence and predictors of patient nonadherence to acute pain therapy at home after day surgery.

METHODS

Patients

This prospective longitudinal cohort study was approved by the Institutional Ethics Committee of the Maastricht University Medical Center, and all patients gave informed consent to participate. All patients undergoing day surgery were eligible to participate, regardless of the type of surgery. Exclusion criteria were (1) age < 18 years, (2) inability to express themselves, (3) visual dysfunction, or (4) insufficient understanding of the Dutch language.

Questionnaires

Patients were asked to complete 2 successive questionnaire packages.

First, a baseline questionnaire package was used to measure demographics (eg, age, gender, work status, highest level of education), preoperative pain variables, psychological variables, previous surgery (related or not to the current surgery), and baseline quality of life (QOL). Preoperative pain variables included average preoperative pain intensity, expected postoperative pain intensity by the patient, interference of preoperative pain with daily activities, and preoperative analgesic use (yes/no). For measurements related to pain, an 11-point numeric rating scale (NRS; 0 = no pain or interference of pain with daily activities, and 10 = worst pain or interference imaginable) was used. Based on recent literature, we defined moderate postoperative pain as an NRS score of > 3 and severe postoperative pain as an NRS score of > 5 in this study.[20,21] Psychological

variables (ie, catastrophic thinking, personality trait optimism, fear of potential short- and long-term consequences of surgery) were analyzed based on 3 validated questionnaires, respectively: the Pain Catastrophizing Scale (PCS), Life Orientation Test Revised (LOT-R), and Surgical Fear Questionnaire (SFQ).[22–25] For the PCS and LOT-R, shortened versions were used to minimize patient burden.[22,26] The EuroQol (EQ-5D) questionnaire was used to analyze QOL.[27]

Second, a follow-up questionnaire package was used to measure adherence prescribed to pain medication, postoperative pain variables, postoperative QOL, and quality of recovery. The occurrence of postoperative nausea, type of prescribed analgesics, use of not-prescribed analgesics, and number of postoperative healthcare visits were also monitored. To measure adherence to prescribed pain medication, patients were asked if they had used their analgesic medication as prescribed during the first 4 postoperative days, to which they responded "yes," "yes, sometimes," or "no." Postoperative pain variables included level of average acute postoperative pain over the first 4 postoperative days and origin (related or unrelated) of postoperative pain, interference of postoperative pain with daily activities, patient satisfaction with pain treatment, and percentage of pain relief by pain treatment. Finally, quality of recovery was measured with the 1-item global surgical recovery (GSR) index. The GSR index represents a single question about the extent to which patients considered themselves to be recovered from surgery ("if 100% recovery means your health is back to the same level as it was before the surgery, what percentage of recovery are you at now?").[22,28]

Procedure

Between November 2008 and April 2010, patients planned for day surgery and presenting at the outpatient clinic for preoperative assessment at the Maastricht University Medical Center, were asked to participate. The purpose and methods of the study were explained to the patient by the anesthesiologist or physician assistant performing the assessment. If consent was obtained, the patient received an envelope containing an informative letter about the study, the 2 questionnaire packages, and 2 return envelopes. Patients also received a standardized prescription for postoperative analgesics (ie, acetaminophen 1,000 mg 4 times a day, and acetaminophen/tramadol 650/75 mg 4 times a day). Furthermore, patients received verbal and written instructions to start with acetaminophen and to switch to acetaminophen/tramadol in case of insufficient analgesia.

Patients were instructed to complete the baseline questionnaire package 1 week before the surgical procedure. Patients who did not return this baseline questionnaire package were considered to be unwilling to participate, and no further attempts to contact them were made. The follow-up questionnaire package had to be completed at the fourth day after surgery. Patients who returned the baseline questionnaire package but did not return the follow-up questionnaire package were reminded by regular mail or telephone. Only patients who returned both the baseline and follow-up questionnaire packages were included into our analyses. All further clinical information (eg, American Society of Anesthesiologists [ASA] physical status, surgical procedure, type of anesthesia, and duration of the procedure) was acquired by systematic chart review.

Outcome Measures

The main outcome variable in this study was analgesic nonadherence. The level of analgesic adherence was defined according to the patient's response to the questionnaire item "analgesia use as prescribed": full adherence, "yes" (category 1); partial adherence, "yes, sometimes" (category 2); nonadherence, "no" (category 3).

Statistical Analysis

All baseline characteristics were presented as mean (standard deviation), median (25th to 75th percentile), or absolute number (percentage). To assess baseline differences between the 3 adherence groups, we used analysis of variance (ANOVA), Kruskal-Wallis tests, and chi-square tests. For the main analyses, we dichotomized the 3 adherence groups into nonadherence (category 3) and adherence (category 1 and 2). For the prediction of nonadherence, we performed bivariate and multivariate logistic regression analyses, with nonadherence as the dependent variable. Potential predictors were entered in the multivariate model using stepwise backward elimination (criterion $P < 0.10$). Age and sex were forced in the model, irrespective of statistical significance. An initial regression model was created with the preoperative variables education level, employment status, ASA classification, preoperative pain intensity, preoperative pain interference, expected postoperative pain intensity, preoperative analgesic use,

fear of short- and long-term aspects of surgery, pain catastrophizing, optimism, and QOL. In the final regression model, the initial model was expanded by the per- and postoperative variables duration of surgery, type of anesthesia, postoperative pain, postoperative pain interference, and postoperative nausea. A final significance level of $P < 0.05$ was chosen. To assess the ability of both the initial and final model to discriminate between adherent and nonadherent patients, the area under the curve (AUC) was calculated.

To prevent a potential loss of statistical power and precision, we used multiple imputation to impute any variables that were incompletely observed. The number of imputations was set to 10. Presented patient data in the results are based on the original data. The statistical results were pooled using Rubin's rules, except for *F* and chi-square distributed statistics. These were pooled using the method described by Allison.[29] Analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, U.S.A.). The pooling of *F* and chi-square statistics was performed in R version 3.3.3, The R Foundation (Vienna, Austria) using the miceadds package.

RESULTS

General Characteristics

During the study period, between November 2008 and April 2010, 2,500 patients were invited to participate; 1,396 patients (56%) returned the baseline questionnaire. Ninety-two percent of these patients (n = 1,282) returned the follow-up questionnaire, of which 34 patients were excluded. This resulted in data of 1,248 patients for statistical analysis (Figure 1).

Baseline patient characteristics, including socio-economic status, psychological parameters, preoperative QOL, and preoperative pain characteristics are shown in Table 1, stratified by groups based on adherence. Mean (SD) age of all patients was 52.2 (14.6) years, 707 were female, and 541 were male. Most patients were classified as ASA I or II.

Baseline analyses revealed that, in general, both full and partial adherence groups showed the most similarities, as opposed to the nonadherence group. Based on these findings, further statistical testing was performed comparing the nonadherence group with the combined full and partial adherence group.

The nonadherence group differed significantly from the combined full and partial adherence group with regard to sex, employment status, QOL, surgical fear, pain catastrophizing, expected pain, preoperative pain intensity, preoperative pain interference, and preoperative analgesic use (see Table 1).

The nonadherence group differed also significantly from the combined full and partial adherence group with regard to duration of surgery, postoperative pain, postoperative pain interference, type of prescribed analgesic used, satisfaction with pain treatment, use of other than prescribed analgesics, origin of pain, postoperative nausea, GSR, and QOL (Table 2).

Prevalence of Analgesic Nonadherence

From a total of 1,248 patients, 706 were fully adherent (56.6%), 250 were partially adherent (20.0%), and 270 were nonadherent (21.6%) (see Table 1). Data on adherence was missing in 22 patients (1.8%). The level of nonadherence for each NRS score of average postoperative pain during the study period is presented in Figure 2. Almost 60% of all patients with an NRS score of 0 were nonadherent. The proportion of nonadherent patients decreased as average pain intensity increased up to an NRS score of 6. At pain intensity levels above a score of 6, the proportion of nonadherence increased again. However, in absolute numbers nonadherence in patients with high pain scores is rather rare. Nonadherence was absent at the highest NRS level of 10. Additional results on adherence, postoperative pain, and postoperative nausea per homogenous surgical group, containing at least 20 procedures, are provided in Table S1.

Of all patients with moderate postoperative pain, 35 patients (12.5%) were nonadherent (2.8% of total population) and 67 patients (24.1%) were partially adherent (5.4% of total population). In the severe pain group, still 20 patients (6.5%) were nonadherent (1.6% of total population) and 49 patients (16.0%) were partially adherent (3.9% of total population). In the combined moderate-to-severe pain group, 9.4% and 19.8% of all patients were nonadherent or partially adherent, respectively.

Prevalence of Use of Other than Prescribed Analgesics and Relationship Between Postoperative Pain Intensity and Use of Other than Prescribed Analgesics

The highest proportion of patients who reported the use of other analgesics (paracetamol, nonsteroidal anti-inflammatory drugs or opioids) than prescribed was

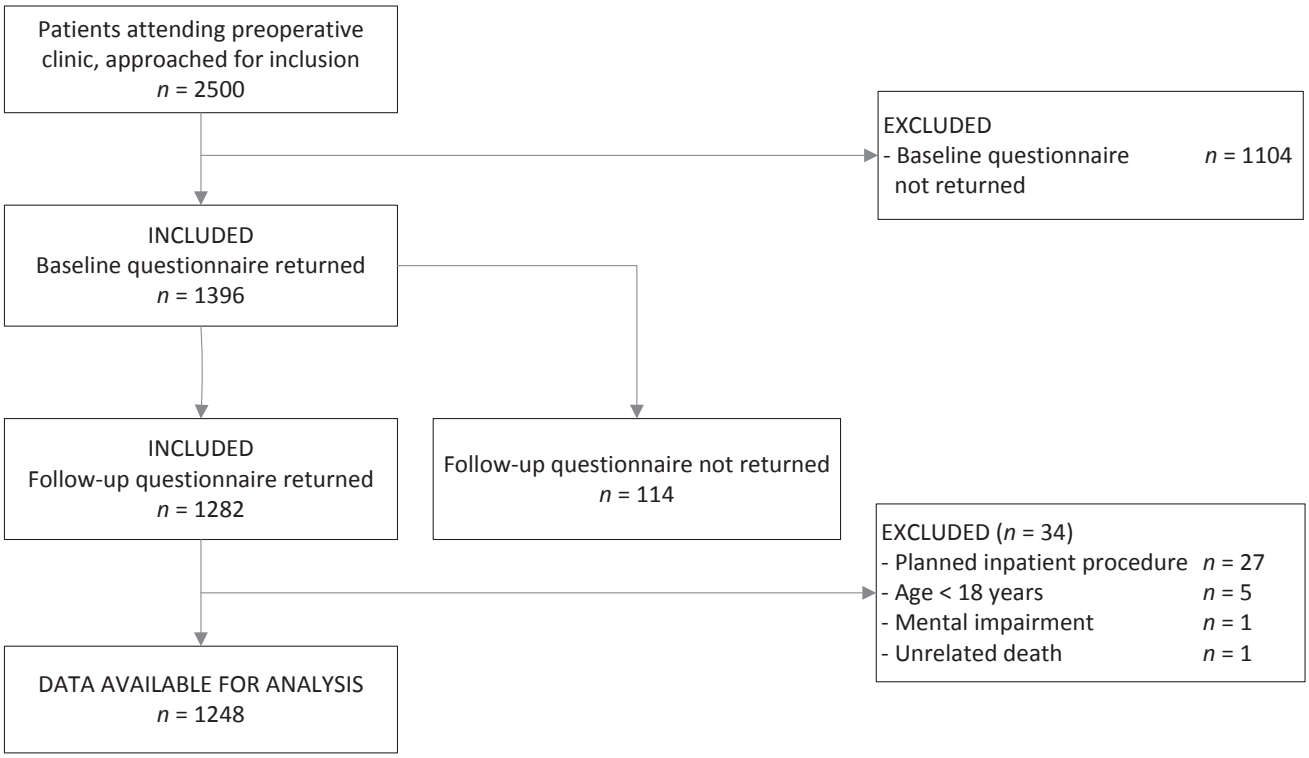

Figure 1. Flowchart depicting the inclusion and exclusion.

found in the nonadherence group (see Table 2). It is unknown whether the use of analgesics other than those prescribed was based on self-administration of over-the-counter medication, or based on prescription by other healthcare professionals such as the general practitioner.

Furthermore, other than prescribed analgesics were used by 9.5% of all patients with mild pain intensity (NRS score of 1 to 3; $n = 631$). A gradual increase in the proportion of patients using other than prescribed analgesics was observed in the moderate pain group ($n = 280$; 17.9%) and the severe pain group ($n = 306$; 22.9%).

Bivariate Logistic Regression Analyses

Bivariate analyses showed male gender, high educational level (vs. low), paid work (vs. voluntary work), low short-term and long-term surgical fear, and high QOL to have a positive association with analgesic nonadherence. All preoperative pain determinants (ie, preoperative pain, preoperative analgesic use, higher expected pain, and high levels of pain interference with daily activities) showed a negative association with nonadherence.

A short duration of surgery, low satisfaction with pain treatment, absence of postoperative nausea, high QOL, and high GSR showed a positive association with analgesic nonadherence. Postoperative pain and high levels of pain interference with daily activities showed a negative association with nonadherence.

Multivariate Logistic Regression Analysis

An initial regression model created with the preoperative variables showed, after stepwise backward elimination, low preoperative pain, low preoperative expectations of pain, and low fear of short-term effects of surgery to be the most important predictors of nonadherence (Table 3). This resulted in a model with an AUC of 0.66.

After extending the initial model with per and postoperative variables, the final regression model showed short duration of surgery and low levels of postoperative pain to be the most important predictors of nonadherence (see Table 3). None of the baseline predictors remained significant in this final model. This resulted in a model with an AUC of 0.77.

DISCUSSION AND CONCLUSIONS

This is the first large prospective cohort study to date assessing both prevalence and possible predictors of

Table 1. Baseline Data per Group: Full, Partial, and No Adherence

Baseline Measures	Full Adherence $n = 706$	Partial Adherence $n = 250$	No Adherence $n = 270$	P
Age (years)	51.5 (14.8)	53.4 (14.2)	52.4 (14.3)	0.198
Female	406 (58%)	150 (60%)	135 (50%)	0.011
Education				
Low	55 (8%)	14 (6%)	13 (5%)	0.085
Middle	508 (73%)	175 (71%)	188 (69%)	
High	132 (19%)	58 (23%)	69 (26%)	
Missing	11	3	0	
Employment status				
Paid job	362 (51%)	112 (45%)	152 (56%)	0.048
Voluntary/unpaid work	118 (17%)	40 (16%)	31 (12%)	
Unemployed	225 (32%)	98 (39%)	87 (32%)	
Missing	1	0	0	
ASA classification				
I	361 (52%)	120 (49%)	141 (53%)	0.224
II	294 (43%)	117 (47%)	118 (45%)	
III	37 (5%)	9 (4%)	6 (2%)	
Missing	14	4	5	
EQ-5D (−0.24 to 1.0)	0.76 (0.24)	0.76 (0.23)	0.81 (0.21)	0.009
EQ-5D health status (0 to 100)	72 (18)	72 (18)	75 (18)	0.055
Surgical fear (short-term, 0 to 40)	15.5 (9.8)	14.6 (9.2)	11.6 (9.1)	< 0.001
Surgical fear (long-term, 0 to 40)	10.5 (9.0)	10.9 (8.4)	8.1 (7.2)	< 0.001
Pain catastrophizing (6 to 30)	12.9 (4.3)	13.0 (4.1)	12.2 (4.0)	0.067
Optimism (4 to 20)	14.2 (2.6)	13.9 (2.5)	14.3 (2.6)	0.268
Expected pain (0 to 10)	4 (2 to 6)	4 (2 to 6)	3 (1 to 5)	< 0.001
Preoperative pain (0 to 10)	3 (0 to 6)	2 (0 to 5)	0 (0 to 4)	< 0.001
Pain interference (0 to 10)	2 (0 to 5)	1.5 (0 to 5)	0 (0 to 4)	< 0.001
Preoperative analgesic use	204 (29%)	58 (24%)	43 (16%)	< 0.001

$N = 1,248$. Values are mean (SD), number (%), or median (25th to 75th percentile).
Original data on adherence of 22 patients are missing; baseline data not shown. Adherence was defined according to the patient's response to the questionnaire item "analgesia use as prescribed": full adherence, "yes"; partial adherence, "yes, sometimes"; nonadherence, "no."
EQ-5D health status: Euroqol quality of life; surgical fear: Surgical Fear Questionnaire short- and long-term subscale; pain catastrophizing: Pain Catastrophizing Scale, items 5 and 12 for Helplessness, items 9 and 11 for Rumination, and items 6 and 13 for Magnification; optimism: Life Orientation Test revised, items 4, 7, 9, and 10; baseline pain: average pain last week, numeric rating scale (NRS); pain interference: impact pain on daily activities last week, NRS; expected pain: expected pain 4 days after surgery, NRS.
P value: comparison of the noncompliance group with the combined groups full and partial compliance. Statistical testing of pooled results, independent *t*-test, Mann–Whitney *U* test, or chi-square, $P < 0.05$.

patient nonadherence to pharmacological acute pain therapy at home after day surgery. Possible predictors included patient characteristics, type and duration of surgery and anesthesia, pre- and postoperative pain-related variables, recovery characteristics, and social and psychological factors.

The results of the present study suggest that nonadherence and partial adherence to pharmacological acute pain therapy after day surgery are relatively high (21.6% and 20.0%, respectively). Furthermore, our study showed a strong and inverse relation between analgesic nonadherence and postoperative pain intensity. Consequently, analgesic nonadherence and partial adherence in patients with moderate to severe pain is less common (9.4% and 19.8%, respectively). Finally, short duration of surgery also predicted nonadherence.

Our data are in line with recent literature on analgesic nonadherence in chronic pain patients, as nonadherence rates in this patient population also range from 8% to 62%, with a weighted mean of 40%.[30] Data on the relationship between pain intensity and nonadherence in chronic pain patients are conflicting.[17,30] In most studies, pain intensity has been shown to be negatively associated with nonadherence in chronic pain patients.[31–34] On the other hand, pain intensity has also been documented to be positively associated with nonadherence in chronic pain patients.[35,36] Finally, one study could not prove an association between chronic pain level and medication nonadherence.[37] One study that also investigated the relationship between acute postoperative pain intensity and analgesic nonadherence also found a strong inverse relationship.[17]

Our data suggest that nonadherent patients are more inclined to take other than prescribed analgesics. Furthermore, we noted a positive association between acute postoperative pain intensity and the use of nonprescribed analgesics. A possible explanation for these findings might be that patients who experienced insufficient pain relief or adverse effects from prescribed pain medication were willing to stop their prescribed pain medication and/or to use other pain medication, such as over-the-counter medication or that prescribed by other healthcare

Table 2. Per- and Postoperative Results per Group: Full, Partial, and No Adherence

	Full Adherence $n = 706$	Partial Adherence $n = 250$	No Adherence $n = 270$	P
Duration of surgery (minutes)	52.3 (35.3)	45.2 (29.4)	40.9 (32.4)	< 0.001
Type of anesthesia				
General	571 (81%)	189 (76%)	210 (78%)	0.350
Locoregional	95 (13%)	47 (19%)	44 (17%)	
Combined general and locoregional	40 (6%)	13 (5%)	14 (5%)	
Missing	0	1	2	
Postoperative pain (0 to 10)	4 (3 to 6)	3 (2 to 5)	2 (0 to 3)	< 0.001
Pain interference (0 to 10)	5 (3 to 8)	4 (2 to 7)	1.5 (0 to 5)	< 0.001
Prescribed analgesic used				
Not	1 (< 1%)	0	269 (99%)	< 0.001
Paracetamol	453 (65%)	183 (74%)	1 (< 1%)	
Zaldiar	96 (14%)	26 (11%)	0	
Paracetamol and zaldiar	150 (21%)	38 (15%)	0	
Missing	6	3	0	
Pain relief (0% to 100%)	70 (50 to 80)	70 (50 to 90)	NA	NA
Satisfaction with pain treatment				
Very unsatisfied	76 (11%)	28 (11%)	21 (8%)	< 0.001
A little or moderately satisfied	186 (27%)	44 (18%)	12 (4%)	
Very satisfied	352 (50%)	118 (48%)	39 (15%)	
Not applicable (no/negligible pain)	85 (12%)	57 (23%)	194 (73%)	
Missing	7	3	4	
Use other analgesics	100 (14%)	15 (6%)	63 (24%)	< 0.001
Origin of pain				
Not surgery-related	23 (4%)	5 (2%)	7 (3%)	< 0.001
Surgery-related	435 (63%)	122 (51%)	64 (25%)	
Unknown	36 (5%)	20 (8%)	9 (3%)	
Not applicable (no pain)	193 (28%)	93 (39%)	177 (69%)	
Missing	19	10	13	
Postoperative nausea	217 (31%)	62 (25%)	45 (17%)	< 0.001
Global surgical recovery (0% to 100%)	58.8 (24.1)	65.2 (22.1)	73.0 (26.2)	
EQ-5D (−0.59 to 1.0)	0.63 (0.30)	0.71 (0.24)	0.79 (0.23)	< 0.001
EQ-5D health status (0 to 100)	69 (19)	73 (16)	78 (17)	< 0.001
Healthcare visits				
0	640 (91%)	234 (93%)	254 (94%)	0.301
1	46 (6%)	12 (5%)	10 (4%)	
> 1	20 (3%)	4 (2%)	6 (2%)	

$N = 1,248$. Values are mean (SD), number (%), or median (25th to 75th percentile).
Original data on adherence of 22 patients are missing (baseline data not shown). Adherence was defined according to the patient's response to the questionnaire item "analgesia use as prescribed": full adherence, "yes"; partial adherence, "yes, sometimes"; nonadherence, "no."
Pain: average pain over the first 4 postoperative days, numeric rating scale (NRS); pain interference: impact pain on daily activities over the first 4 postoperative days, NRS; pain relief: pain relief as result of medication, over the past 24 hours, 4 days after surgery (0% to 100%; in the no adherence group, 76% indicated not applicable; therefore, no results are shown for this group); use other analgesia: paracetamol, NSAID, or opioid; EQ-5D health status: Euroqol quality of life 0 to 100; healthcare visits: post-discharge visit to general practitioner, emergency room, or specialist because of pain.
P value: comparison of the noncompliance group with the combined groups full and partial compliance. Statistical testing of pooled results, independent t-test, Mann–Whitney U test, or chi-square, $P < 0.05$.

professionals. It has to be pointed out that the combined use of prescribed and nonprescribed analgesics carries the risk of serious adverse drug events due to overdose and toxicity as for instance with paracetamol.

Another primary goal of this study was to identify predictors of patient nonadherence to acute pain therapy at home after day surgery. Bivariate analysis of all preoperative variables showed male gender, high educational level, paid work, low short-term and long-term surgical fear levels and high EQ-5D health status to be positively associated with nonadherence. The preoperative pain variables (ie, preoperative pain, preoperative analgesic use, higher expected pain, and high levels of pain interference with daily activities) were shown to be negatively associated with nonadherence. The observed association between high educational level and nonadherence is in line with a previous study on nonadherence in chronic pain patients.[30] Highly educated patients may use more active coping strategies or self-medication to improve their pain symptoms and/or may have more concerns about prescribed pain medication.

Bivariate analysis of all perioperative variables showed short duration of surgery, low satisfaction with pain treatment, absence of postoperative nausea, high

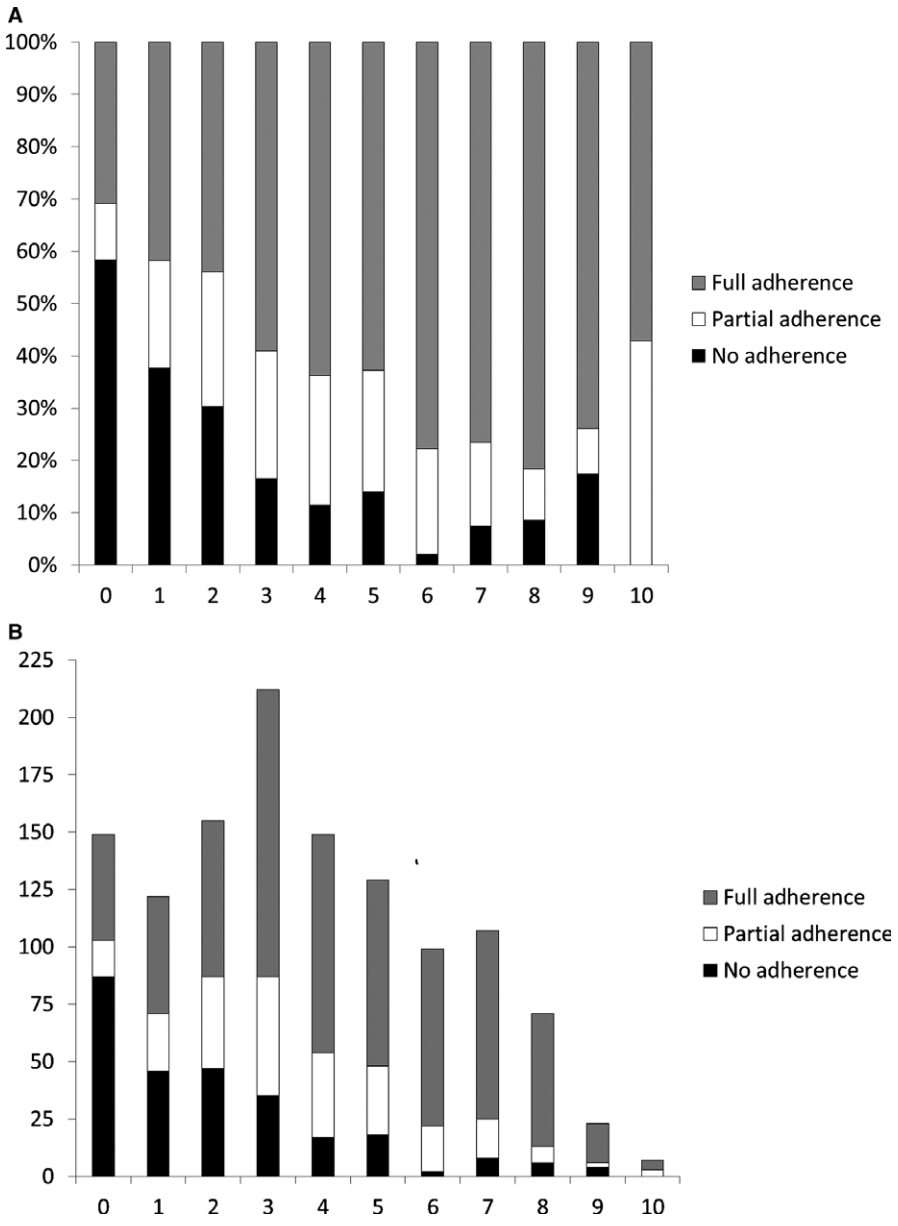

Figure 2. Adherence in relation to postoperative pain score NRS 0 to 10. (A) Percentage. (B) Patient numbers.

EQ-5D health status, and high GSR to be positively associated with analgesic nonadherence. Postoperative pain and high levels of pain interference with daily activities were negatively associated with nonadherence. The negative association between analgesic nonadherence and postoperative nausea is rather surprising. One could presume that patients would stop taking their prescribed analgesic (acetaminophen/tramadol) if they experienced postoperative nausea as an adverse effect. Nevertheless, patients with high pain scores were willing to continue their analgesic therapy despite the associated adverse effects. Furthermore, pain itself has been associated with postoperative nausea.[38] Consequently, the apparent negative association between postoperative nausea and nonadherence can be explained by the negative association between pain intensity and nonadherence. Our logistic regression model confirmed this hypothesis as postoperative nausea fell out of this final model.

A model created with all the preoperative variables to preoperatively predict nonadherence showed that low preoperative pain intensity, low preoperative expectations of pain, and low fear of short-term effects of surgery were the most important preoperative predictors of nonadherence. The predictive power of these 3 variables in the preoperative model is not surprising

Table 3. Prediction of Nonadherence: Multivariate Logistic Regression Models

	Initial Model (Preoperative)		Final Model (Perioperative)	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Intercept	0.80 (0.42 to 1.53)	0.505	3.09 (1.48 to 6.45)	**0.003**
Age	1.00 (0.99 to 1.01)	0.588	0.99 (0.98 to 1.00)	0.094
Sex				
Female	Reference		Reference	
Male	1.29 (0.97 to 1.72)	0.083	1.34 (0.99 to 1.82)	0.057
ASA classification				
ASA I	Reference		Reference	
ASA II	1.01 (0.73 to 1.39)	0.952	0.98 (0.70 to 1.37)	0.891
ASA III	0.42 (0.17 to 1.03)	0.057	0.46 (0.18 to 1.18)	0.106
Preoperative pain	0.93 (0.88 to 0.99)	**0.015**	1.00 (0.94 to 1.06)	0.897
Expected pain	0.85 (0.79 to 0.92)	**< 0.001**	0.95 (0.88 to 1.03)	0.239
Short-term surgical fear	0.98 (0.96 to 1.00)	**0.025**	0.99 (0.97 to 1.00)	0.109
Duration of surgery	NA		0.99 (0.99 to 1.00)	**0.001**
Postoperative pain	NA		0.73 (0.65 to 0.82)	**< 0.001**
Postoperative pain interference	NA		0.93 (0.86 to 1.01)	0.087

Odds ratio and 95% confidence interval (CI) have been rounded to 2 decimals. Area under the curve (AUC) of model 1 = 0.66; model 2 = 0.77.
ASA, American Society of Anesthesiologists.
Bold indicates results of the logistic regression analysis for prediction of nonadherence. An initial regression model was created with the preoperative variables. The final model was extended with per- and postoperative variables.

since they all have a strong positive association with postoperative pain intensity.[39,40]

After extending the preoperative model with Per- and postoperative variables, the final model showed low postoperative pain level to be the most important predictor of analgesic nonadherence together with a short-duration surgery. All the preoperative variables lost significance in this final model. The inverse correlation between length of surgery and analgesic nonadherence is also expected since longer operations are associated with more enduring nociceptive input, which may increase the chance of central sensitization, and subsequently persistent pain.[22]

Improving adherence to pharmacological pain treatment is clinically relevant in those patients with moderate to severe pain. Interventions to improve analgesic adherence include better patient education, telephone follow-up, electronic reminders, and monitoring systems (eg, short message service text messaging and real-time medication monitoring linked to smart pill containers).[30,41] Regular assessments of analgesic adherence by telephone follow-up have the advantage that it can be combined with assessments of pain relief by prescribed analgesics. If necessary, analgesic therapy can be tailored to individual patient needs.

The present study also has some limitations. Firstly, we didn't specifically ask patients the reason for analgesic nonadherence. As a consequence, we are not able to differentiate between unintentional or intentional nonadherence. Therefore, we can only speculate on the exact relationship between nonadherence and the factors associated with it. For example, analgesic nonadherence may be associated with male sex because male patients have an increased risk for forgetting to take their medication (unintentional) or because male patients experience less pain than women or are more unwilling to take their medication because of side-effects (intentional). Secondly, this is a questionnaire-based survey, and the response rate was 51% for both the baseline and follow-up questionnaire. Hence, there is a possible danger of selection bias. Still, the response rate is similar to those of other questionnaire-based surveys. Thirdly, we used self-report to measure medication nonadherence. This is a subjective method that tends to underestimate nonadherence.[42] In contrast, objective methods, such as urine analysis, are generally more reliable for monitoring nonadherence. These objective methods, however, are expensive and difficult to implement in a home setting, and furthermore, they may partly be considered as an adherence intervention.[30] There is no gold standard approach to the measurement of nonadherence as all methods have pros and cons. Nevertheless, a patient-centered approach with patient-reported information as a measure of medication adherence has recently been advocated.[41] Fourthly, we did not clearly differentiate between medication underuse and overuse, a distinction often made in medication nonadherence in chronic patients.[13,30] In our patient cohort, medication nonadherence mainly refers to medication underuse. The use of nonprescribed analgesics may partially refer to medication overuse. Finally, patients enrolled in the present study were

postoperatively treated with a combination of paracetamol and a weak opioid, tramadol. Most postoperative regimens in the United States, however, are based on strong opioids. Therefore, the generalizability of our results can be questioned. More specifically, the threat of overuse and subsequent opioid addiction because of a feeling of well-being may be more present in the United States.

In conclusion, our data demonstrate that analgesic nonadherence and partial adherence in a large cohort of day surgery patients are common (21.6% and 20.0%, respectively). Analgesic nonadherence and partial adherence in day surgery patients with moderate to severe pain are less common (9.4% and 19.8%, respectively). Low postoperative pain intensity and short duration of surgery were the most important predictors of analgesic nonadherence. The most important preoperative predictors for analgesic nonadherence were low preoperative pain intensity, low preoperative expectations of pain, and low fear of short-term effects of surgery.

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CONFLICT OF INTEREST

The authors state that they don't have any conflict of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Adherence, Pain, and Nausea per type of surgery.

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