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Prevalence and predictors of patient non-adherence 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 non-adherence 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 two time points: one week preoperatively and four days postoperatively. Primary outcome parameter was analgesic non-adherence and was defined as follows: Full adherence: analgesia use as prescribed “Yes”, partial adherence: analgesia use as prescribed “Yes sometimes”, non-adherence: analgesia use as prescribed “No”. Bivariate and multivariate logistic regression analyses were performed to identify predictors of analgesic non-adherence.
Results
A total of 1248 patients were included. The prevalence of analgesic non-adherence and partial adherence was 21.6% and 20.0% respectively in the total study population but dropped to respectively 9.4% and 19.8% in patients with moderate to severe pain. Low postoperative pain intensity and short duration of surgery were the most important predictors of analgesic non-adherence. The most important preoperative predictors for analgesic non-adherence were low preoperative pain intensity, low preoperative expectations of pain, and low fear of short-term effects of surgery.
Conclusion
Analgesic non-adherence and partial adherence is common after day surgery but decreases as average pain intensity increases. Patients at risk for analgesic non-adherence can be identified during the preoperative period based on preoperative pain intensity, preoperative expectations of pain, and fear of surgery.

Introduction

Despite increased awareness and improvements in postoperative pain management over the last decades, the prevalence of outpatients suffering moderate to severe acute postoperative pain at home still remains high and varies from 9-40%.[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 out-patients.[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 pose that “adherence presumes an agreement between prescriber and patient about the prescriber's recommendations”.[13,14]

There are many causes of non-adherence but they fall into two overlapping categories: intentional and unintentional.[14] Unintentional non-adherence 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 non-adherence 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 non-adherence in patients with chronic pain is a frequent problem and a well-studied topic in literature.[13,15,16] In contrast, analgesic non-adherence 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 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 non-adherence after day surgery may provide new insights for patient counselling, 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 non-adherence 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 XXX 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. patients 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 two successive questionnaire packages.

First, a baseline questionnaire package was used to measure demographics (e.g. 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 > 3 and severe postoperative pain as an NRS > 5 in this study.[20,21] Psychological variables (i.e. catastrophic thinking, personality trait optimism, fear of potential short and long-term consequences of surgery) were analyzed based on three validated questionnaires, respectively the Pain Catastrophizing Scale (PCS), the 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 the number of postoperative health care 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 four postoperative days: '1. yes, 2. Yes, sometimes or 3. no'. Postoperative pain variables included level of average acute postoperative pain over the first four 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 the 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 XXX 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 two questionnaire packages, and two return envelopes. Patients also received a standardized prescription for postoperative analgesics (i.e. acetaminophen 1000 mg four times a day, and acetaminophen/tramadol 650/75 mg four 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 one 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 the 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 the follow-up questionnaire packages were included into our analyses. All further clinical information (e.g. 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 is analgesic non-adherence. The level of analgesic adherence is defined as follows: Full adherence: analgesia use as prescribed “Yes” (category 1), partial adherence: analgesia use as prescribed “Yes sometimes” (category 2), non-adherence: analgesia use as prescribed “No” (category 3).

Statistical analysis

All baseline characteristics were presented as mean (standard deviation), median (25th-75th percentile), or absolute number (percentage). To assess baseline differences between the three adherence groups, we used analysis of variance (ANOVA), Kruskal-Wallis tests, and Chi-square tests. For the main analyses, we dichotomized the three adherence groups into non-adherence (category 3) and adherence (category 1 and 2). For the prediction of non-adherence, we performed bivariate and multivariate logistic regression analyses, with non-adherence as 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 initial and final model to discriminate between adherent and non-adherent 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 ten. 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. Armonk, NY, USA.. The pooling of F and Chi-square statistics was performed in R version 3.2.3 using the miceadds package.

Results

General characteristics

During the study period, between November 2008 and April 2010, 2500 patients were invited to participate. 1396 patients (56%) returned the baseline questionnaire. Ninety-two percent of these patients (N = 1282) returned the follow-up questionnaire, of which 34 patients were excluded. This resulted in data of 1248 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), 707 were female, 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 non-adherence group. Based on these findings, further statistical testing was performed comparing the non-adherence group with the combined full and partial adherence group.

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

The non-adherence group differed also significantly from the combined full and partial adherence groups 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 non-adherence

From a total of 1248 patients, 706 were fully adherent (56.6%), 250 were partially adherent (20.0%) and 270 were non-adherent (21.6%) (Table 1). Data on adherence was missing in 22 patients (1.8%). The level of non-adherence for each NRS score of average postoperative pain during the study period is presented in Figures 2a and 2b. Almost 60% of all patients with an NRS of 0 were non-adherent. The proportion of non-adherent patients decreased as average pain intensity increased up to an NRS of 6. At pain intensity levels above six the proportion of non-adherence increased again. However, in absolute numbers non-adherence in patients with high pain scores is rather rare. Non-adherence 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 the supplementary file.

Of all patients with moderate postoperative pain, 35 patients (12.5%) were non-adherent (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 non-adherent (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, respectively 9.4% and 19.8% of all patients were non-adherent or partially adherent.

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, NSAID´s or opioids) than prescribed was found in the non-adherence group (Table 2). It is unknown whether the use of other analgesics than prescribed was based on self-administration of over-the-counter medication, or based on prescription by other health care professionals such as the general practitioner.

Furthermore, other than prescribed analgesics were used by 9.5% of all patients with mild pain intensity (NRS 1 – 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 (versus low), paid work (versus voluntary work), low short-term and long-term surgical fear and high QOL to have a positive association with analgesic non-adherence. All preoperative pain determinants (i.e. preoperative pain, preoperative analgesic use, higher expected pain and high levels of pain interference with daily activities) showed a negative association with non-adherence.
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 non-adherence. Postoperative pain and high levels of pain interference with daily activities showed a negative association with non-adherence.

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

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

Our data suggests that non-adherent 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 non-prescribed 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 or prescribed by other health care professionals. It has to be pointed out that combined use of prescribed and non-prescribed 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 non-adherence 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 non-adherence. The preoperative pain variables (i.e. preoperative pain, preoperative analgesic use, higher expected pain and high levels of pain interference with daily activities) were shown to be negatively associated with non-adherence. The observed association between high educational level and non-adherence is in line with a previous study on non-adherence 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 toward prescribed pain medication.

Bivariate analysis of all perioperative variables showed short duration of surgery, low satisfaction with pain treatment, absence of postoperative nausea, high EQ-5D health status and high GSR to be a positively associated with analgesic non-adherence. Postoperative pain and high levels of pain interference with daily activities were negatively associated with non-adherence. The negative association between analgesic non-adherence 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 non-adherence can be explained by the negative association between pain intensity and non-adherence. 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 non-adherence 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 non-adherence. The predictive power of these 3 variables in the preoperative model is not surprising 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 non-adherence 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 non-adherence 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, e.g. 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 non-adherence. As a consequence, we are not able to differentiate between unintentional or intentional non-adherence. Therefore, we can only speculate on

the exact relationship between non-adherence and the factors associated with it. For example, analgesic non-adherence may be associated with male sex because male patients have an increased risk of 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 baseline and follow-up questionnaire. Hence, there is a possible danger of selection bias. Still, the response rate is similar to other questionnaire-based surveys. Thirdly, we used self-report to measure medication non-adherence. This is a subjective method which tends to underestimate non-adherence.[42] In contrast, objective methods, such as urine analysis, are generally more reliable for monitoring non-adherence. 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 non-adherence 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 didn´t clearly differentiate between medication underuse and overuse, a distinction often made in medication non-adherence in chronic patients.[13,30] In our patient cohort, medication non-adherence mainly refers to medication underuse. The use of non-prescribed 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 feeling of wellbeing may be more present in the United States.

In conclusion, our data demonstrate that analgesic non-adherence and partial adherence in a large cohort of day surgery patients is common (21.6% and 20.0% respectively). Analgesic non-adherence and partial adherence in day surgery patients with moderate to severe pain is less common (9.4% and 19.8% respectively). Low postoperative

pain intensity and short duration of surgery were the most important predictors of analgesic non-adherence. The most important preoperative predictors for analgesic non-adherence were low preoperative pain intensity, low preoperative expectations of pain, and low fear of short-term effects of surgery.

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Table 1 Baseline data per group full-partial-no adherence

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

Expected pain (0-10)	4 (2-6)	4 (2-6)	3 (1-5)	<0.001
Preoperative pain (0-10)	3 (0-6)	2 (0-5)	0 (0-4)	<0.001
Pain interference (0-10)	2 (0-5)	1.5 (0-5)	0 (0-4)	<0.001
Preoperative analgesic use	204 (29%)	58 (24%)	43 (16%)	< 0.001

N=1248, original data on adherence of 22 patients are missing: baseline data not shown. Full adherence: analgesia use as prescribed “Yes”, partial adherence: analgesia use as prescribed “Yes sometimes”, no adherence: analgesia use as prescribed “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 (LOT-r) 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 four days after surgery NRS.

Mean (sd), number (%), or median (25^{th}-75^{th} percentile).

P value: comparison of the non-compliance group with the combined groups full and partial compliance. Statistical testing of pooled results, independent t-test, Mann-Whitney U test, or Chi-square, $p < 0.05$.

Table 2 Per- and postoperative results per group full-partial-no adherence

	Full adherence	Partial adherence	No adherence	P
	N 706	N 250	N 270	
Duration of surgery (min.)	52.3 (35.3)	45.2 (29.4)	40.9 (32.4)	<0.001
Type of anaesthesia				0.350
General	571 (81%)	189 (76%)	210 (78%)	
Loco-regional	95 (13%)	47 (19%)	44 (17%)	
Combined general & loco-regional	40 (6%)	13 (5%)	14 (5%)	
Missing	0	1	2	
Postoperative pain (0-10)	4 (3-6)	3 (2-5)	2 (0-3)	<0.001
Pain interference (0-10)	5 (3-8)	4 (2-7)	1.5 (0-5)	<0.001
Prescribed analgesic used				<0.001
Not	1 (<1%)	0	269 (99%)	
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 (0-100%)	70 (50-80)	70 (50-90)	NA	NA
Satisfaction with pain treatment*				<0.001
Very unsatisfied	76 (11%)	28 (11%)	21 (8%)	
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				<0.001

Not surgery-related	23 (4%)	5 (2%)	7 (3%)	
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 (0-100%)*	58.8 (24.1)	65.2 (22.1)	73.0 (26.2)	
EQ-5D (-0.59 – 1.0)	0.63 (0.30)	0.71 (0.24)	0.79 (0.23)	<0.001
EQ-5D health status (0-100)	69 (19)	73 (16)	78 (17)	<0.001
Health care visits				0.301
0	640 (91%)	234 (93%)	254 (94%)	
1	46 (6%)	12 (5%)	10 (4%)	
>1	20 (3%)	4 (2%)	6 (2%)	

N=1248, original data on adherence of 22 patients are missing (baseline data not shown).

Full adherence: analgesia use as prescribed “Yes”, partial adherence: analgesia use as prescribed “Yes sometimes”, no adherence: analgesia use as prescribed “No”.

Pain: average pain over the first four postoperative days, numeric rating scale (NRS). Pain interference: impact pain on daily activities over the first four postoperative days, NRS. Pain relief: pain relief as result of medication, over the last 24 hours, four days after surgery (0-100%); in the group no adherence 76% indicated: not applicable (NA), therefore no results are shown for this group. Use other analgesia: paracetamol, NSAID, or opioid.

EQ-5D health status: Euroqol quality of life 0-100. Health care visits: post-discharge visit to general practitioner, emergency room, or specialist because of pain.

Mean (sd), number (%), or median (25^{th}-75^{th} percentile).

P value: comparison of the non-compliance group with the combined groups full and partial compliance. Statistical testing of pooled results, independent t-test, Mann-Whitney U test, or Chi-square, $p < 0.05$.

Table 3 Prediction of non-adherence. Multivariate logistic regression models

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

Odds ratio and 95% confidence interval (CI), rounded to two decimals.

Area under the curve (AUC) of model 1 = 0.66, of model 2 = 0.77