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# In-hospital opioid consumption, but not pain intensity scores, predict 6-month levels of pain catastrophizing following hepatic resection: a trajectory analysis

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**Significance**: Differences in initial levels of opioid consumption and rates of change in opioid consumption shortly after surgery can help predict long-term psychological responses to pain. Identifying key characteristics associated with initial opioid consumption can lead to the development of cost-effective early interventions targeted to high risk individuals.

**Abstract**

**Background.** The study aims were to model acute pain intensity and opioid consumption trajectories up to 72 hours after open hepatic resection, identify predictors of trajectory membership and examine the association between trajectory memberships and six-month pain and psychological outcomes. This is a long-term analysis of a published randomized controlled trial on the impact of medial open transversus abdominis plane catheters on post-operative outcomes.

**Methods.** A total of 152 patients (89 males; mean age 63.0 [range: 54-72]) completed questionnaires on pain and related characteristics pre-operatively and 6 months post-operatively. Total opioid use was recorded several times over a 72-hour period while self-reported pain intensity scores were collected multiple times until hospital discharge. Analyses were carried out using growth mixture modeling, logistic regression and general linear models.

**Results.** Both pain intensity and opioid consumption showed that a four-trajectory model best fit the data. Patients in the lowest opioid consumption trajectory were more likely to be classified in the constant mild pain intensity trajectory. Age and baseline levels of anxiety significantly predicted opioid trajectory membership while baseline depressive symptoms significantly predicted pain intensity trajectory membership. Patients in the two highest opioid consumption trajectories reported significantly higher levels of pain catastrophizing at six months compared to patients in the other 3 trajectories (all $p < 0.05$).

**Conclusion.** High consumption of opioids after surgery is associated with higher levels of pain catastrophizing six months later. Identification of patients within these trajectories may lead to the development of early interventions targeted to high risk individuals.

**Significance**: Differences in initial levels of opioid consumption and rates of change in opioid consumption shortly after surgery can help predict long-term psychological responses to pain. Identifying key characteristics associated with initial opioid consumption can lead to the development of cost-effective early interventions targeted to high risk individuals.

**Keywords**:

Chronic Pain; Surgery; Analgesics, Opioid; trajectories

**Trial Registry Number**: NCT01960049, Sept 23, 2013; http://clinicaltrials.gov

Chronic post-surgical pain (CPSP) is a common outcome of many types of operations (Bruce and Quinlan 2011). CPSP refers to the presence of pain at the surgery site with an onset following surgery (or worsening of a pre-operative pain after surgery) that lasts for at least 3-6 months, that cannot be attributed to other causes than surgery and that impacts on a patient's quality of life or functioning (Werner and Kongsgaard 2014). Several risk factors for the development of CPSP have been identified (Katz and Seltzer 2009), including poor early postoperative pain experience (Katz 2012; Katz et al., 1996; Katz and Seltzer 2009; Perkins and Kehlet 2000).

Both preoperative pain status and preoperative opioid consumption have been identified as risk factors for the development of CPSP (Schug and Bruce 2017). While this is also true of acute post-surgical pain, fewer articles have been published on the association between perioperative opioid consumption and CPSP outcomes (Katz et al., 2015; Schug and Bruce 2017). Research suggests however that acute post-operative pain and opioid consumption are strongly associated (Lindberg et al., 2017; Maheshwari et al., 2016). Recently, studies have moved beyond simple static measures of acute pain to examine profiles of pain trajectories and how they relate to long-term outcomes (Chapman et al., 2011a; Chapman et al., 2011b; Chapman et al., 2012; Page et al., 2016). It remains to be determined whether specific empirically-derived opioid consumption profiles following surgery might contribute to the prediction of CPSP above and beyond pain intensity.

The overall study aim was to use a latent trajectory-based approach to examine the association between pain and opioid consumption after hepatic resection and CPSP

status, levels of pain disability and psychological distress 6 months later. More specifically, the objectives were to:

(1) Identify and examine subgroup trajectories of cumulative opioid consumption as well as subgroup trajectories of pain intensity at rest over the first 72 hours postoperatively;

(2) Examine degree of association between opioid and pain trajectory membership; and

(3) Examine the association between opioid and pain trajectory membership and 6-month pain and related outcomes.

This is a long-term analysis of a published prospective, longitudinal, multicenter, randomized controlled trial comparing medical open transversus abdominis plane (MOTAP) catheters combined with intra-venous (IV) patient-controlled analgesia (PCA) to IV PCA alone among patients undergoing liver resection using a right subcostal incision (Karanicolas et al., in press).

## Methods

### Study design

Please refer to published study protocol for details (Karanicolas et al., 2014). The Research Ethics Boards from Sunnybrook Health Sciences Centre (178-2013) and University Health Network (12-0493-A) approved this registered trial (http://clinicaltrials.gov NCT01960049, Sept 23, 2013).

### Participants

Participants were eligible for this study if they were scheduled to undergo liver resection through a right subcostal incision. Exclusion criteria included presence of chronic pain or chronic use of opioids, contraindication to local anaesthetic, and having had in the past a right subcostal incision. In addition, patients were withdrawn from study if they did not

receive a right subcostal incision, were intubated for more than four hours postoperatively or re-intubated within 48 hours postoperatively.

Procedures and measures

Procedures and measures relevant to this analysis are described below; please refer to detailed protocol for a comprehensive overview of all measures administered (Karanicolas et al., 2014).

*Recruitment.* Patients were recruited either during their pre-surgical consent visit or the anaesthesia pre-assessment clinic and informed consent was then obtained.

*Baseline information.* Prior to surgery, patients completed self-report questionnaires assessing sociodemographic characteristics, chronic pain history (including presence of chronic pain problems, pain frequency and intensity using the 11-point Numeric Rating Scale (Dworkin et al., 2005) (0 = no pain, 10 = worst possible pain), and pain disability using the Pain Disability Index (PDI) (Chibnall and Tait 1994)), and validated psychological measures including the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995) and the Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002).

*Randomization.* Patients were randomized to the experimental (local anesthetic administered through the MOTAP catheters) or placebo (normal saline solution administered through the MOTAP catheters) groups using a double-blind procedure.

*Surgical procedure and peri-operative information.* Patients underwent liver resection using a right subcostal incision with upper midline extension or limited left subcostal extension if determined necessary by operating surgeon.

*Study intervention.* Once surgery was completed, the trained surgeon inserted two catheters (transversus abdominis plane and posterior rectus space) that was used to administer ropivacaine 0.2% 5mL through each catheter or saline solution. These catheters were removed in the morning post-operative day 3.

Multimodal analgesia algorithm was used in all patients regardless of group allocation. This included celecoxib 200mg taken twice daily orally (if baseline serum creatinine inferior to 90 μmol/L) as well as intravenous patient-controlled-analgesia (PCA) of hydromorphone 0.2mg using a 5-minute lockout period and no background infusion.

*In-hospital post-operative period.* Cumulative morphine equivalent consumption over the first 72 hours postoperatively, taking into account IV PCA as well as any additional IV or oral opioids), taken from medical chart. Pain intensity at rest and with coughing was assessed by a research assistant using the NRS every 8 hours for the first 48 hours and then daily until hospital discharge.

*Long-term outcomes.* Six months postoperatively, patients completed the following questionnaires administered over the phone: PCS, HADS, PDI as well as questions on the status of their post-operative pain (presence/absence, frequency, intensity using the NRS). Patients with pre-existing chronic pain were considered as having chronic post-surgical pain if their post-surgical pain intensity (NRS) and interference (PDI) scores were clinically meaningfully (Farrar et al., 2001) higher than pre-operatively (increase of 2 points on the NRS pain intensity and 20% on the PDI) (Werner and Kongsgaard 2014).

Data analysis

*Obj 1. Cumulative opioid consumption and pain intensity trajectories*

Two separate latent growth mixture modeling (GMM) analyses were run, one to create an opioid consumption trajectory model and the other to create a pain intensity trajectory model. This latent trajectory approach was chosen because it takes into account both inter- and intra-individual variability and groups individuals that share similar profiles in terms of intercept and rates of change over time. This has the advantage of taking into account the dynamic nature of the pain experience and how these early day changes influence long-term outcomes. The goal of this statistical approach is to identify different subgroups of patients that are homogeneous in their initial levels of pain or opioid consumption as well as similar rates of change on this outcome over time.

GMM (Asparouhov and Muthen 2008; Muthen and Asparouhov 2009) carried out using the lcmm package (Proust-Lima et al., 2015) in R (version 3.4.1) (R Core Team 2014) was performed to generate opioid consumption and pain at movement (cough-related) trajectory models over the first 72 hours postoperatively. For each model, this latent approach examines and compares trajectory solutions that differed in terms of number of trajectories, initial level of the outcome, as well as linear and quadratic parameters to capture rates of change on the outcome over time. A total of 16 models for each opioid and pain trajectory models (from 1 to 8 trajectories and presence/absence of a quadratic term) were tested and compared. Model selection was based on fit indices (lowest Akaike Information Criterion and Bayesian Information Criterion) (Akaike 1983), adequacy of trajectories (a minimum of 5% of patients assigned to the smallest class) as well as theoretical soundness and interpretability of trajectories. Following selection of the optimal model, the model was re-run with the inclusion of the treatment

allocation variable as a covariate of the trajectory membership and other baseline predictors that were retained in the final model only if significant ($p < 0.05$).

*Obj 2. Association between opioid consumption and pain intensity trajectories*

Pearson chi-square test was used to examine the degree of association between opioid consumption trajectory membership and pain intensity trajectory membership.

*Obj 3. Association between opioid consumption trajectories, pain intensity trajectories and gender with long-term outcomes*

Logistic regression models were used to examine whether opioid consumption trajectory membership and pain intensity trajectory membership, after controlling for gender, were associated with presence/absence of chronic postoperative pain status at 6 months (model 1), and presence/absence of chronic postoperative pain of moderate to severe intensity (NRS > 3) (model 2).

General linear modeling was used to examine the associations between opioid consumption trajectory membership, opioid consumption trajectory membership, and gender with levels of pain disability at 6 months (PDI).

Multivariate general linear modeling was used to examine the associations between opioid consumption trajectory membership, pain intensity trajectory membership and gender with psychological outcomes at 6 months (PCS, HADS depression subscore, HADS anxiety subscore).

## Results

A total of 480 participants were screened for eligibility criteria between December 2013 and June 2016 and 176 patients were randomized. A total of 152 patients were included in the primary study analysis (see Figure 1 for details).

Patients were primarily male (n=89; 58.82%) with a mean age of 63 years (range: 54-72). Descriptive statistics on key measures for the overall sample are presented in Table 1. Figure 2 shows the cumulative opioid consumption (left panel) and NRS pain at movement scores over the first 72 hours postoperatively according to treatment allocation (intervention vs. placebo). There were statistically significant differences in opioid consumption and pain scores across treatment allocation (Karanicolas et al., 2018) and as such this variable was controlled for in the trajectory models.

### *Opioid and Pain Trajectories*

For each of the opioid and pain trajectory analyses, a total of 16 models were evaluated that differed in terms of number of trajectories (between 1 and 8) as well as presence or absence of a quadratic term. Table 2 shows the model fit for each model tested. For both the opioid trajectory and the pain at movement trajectory models, a four trajectory model (with a linear and quadratic term for the opioid consumption model and with a linear term only for the pain at movement model) best fit the data while ensuring a minimum of 5% of patients belonging to the smallest trajectory.

*Opioid consumption model:* The square root of opioid consumption was used as this variable was positively skewed. Several baseline predictors of opioid trajectory were examined (age, sex, pre-operative pain status, pre-operative use of analgesics, anxiety, depression, pain catastrophizing, cumulative consumption of acetaminophen, celecoxib,

and gabapentin in-hospital, surgical procedure and type of diagnosis) individually and significant individual predictors of trajectory membership were included in the final model. Model controlled for randomization (intervention and placebo). The final model (AIC = 2458.10, BIC = 2531.64) was a 4-trajectory model with a linear and quadratic terms and randomization, age and baseline anxiety level as predictors of class trajectory membership. Patients in Opioid Trajectory 1 had the lowest opioid consumption while patients in Opioid Trajectory 4 had the highest opioid consumption. For all trajectories, there was a significant linear or quadratic effect suggesting their levels of opioid consumption significantly increased over time. The comparative amount of opioid consumption across trajectories remained the same over time (e.g., patients in trajectory # 5 consumed more opioids in the first 12 hours postoperatively and this trend continued up to 72 hours postoperatively).

Results showed that compared to patients in trajectory 4, patients in trajectories 1-3 were significantly older while patients in trajectory 1 had significantly lower levels of baseline anxiety compared to patients in trajectory 4 ($p < 0.05$).

*Pain at movement trajectory model:* The same baseline predictors as for the opioid model were examined (age, sex, pre-operative pain status, pre-operative use of analgesics, anxiety, depression, pain catastrophizing, cumulative consumption of acetaminophen, celecoxib and gabapentin in-hospital, surgical procedure and type of diagnosis) with the addition of cumulative opioid consumption at 72 hours. Final model (AIC = 5018.62, BIC = 5071.31) controlled for randomization (intervention and placebo) and included baseline levels of depression as predictor of trajectory membership. None of

the other baseline predictors tested were significantly associated with pain trajectory membership in the final model ($p > 0.05$).

Patients in Trajectory 1 (constant mild pain) reported minimal pain intensity throughout the first three days postoperatively with no significant changes in intensity levels across time. Similarly, patients in Trajectories 3 (constant mild/moderate pain) and 4 (constant moderate pain) experienced also constant pain over the first three postoperative days but their pain was higher in intensity. Patients in Trajectory 2 (severe pain intensity rapidly decreasing) reported a rapid significant change in their pain intensity level to reach mild pain intensity by the third post-operative day. Results also showed that patients in Trajectory (constant mild pain) had significantly lower levels of baseline depressive symptoms compared to patients in Trajectory 4 (constant moderate pain).

Distribution frequencies of diagnosis per trajectory membership are presented in Table 1. Opioid and pain trajectories are presented in Figure 3.

*Association between Opioid and Pain Trajectory Membership*

Pearson chi-square test showed significant differences between opioid and pain trajectory membership such that patients in the lowest opioid consumption trajectory were more likely to be classified in the constant mild pain trajectory and less likely to be classified in the constant moderate pain trajectory than would be expected by change ($\chi^2$ (df=9) = 33.36; $p < 0.001$). There were no other significant differences; for example, patients in the severe pain intensity rapidly decreasing trajectory were equally distributed across the opioid trajectories (see Table 3).

*6-month Outcomes*

Results of the factorial logistic regression models examining association between opioid and pain trajectory membership and gender with CPSP status at 6 months were significant for presence/absence of CPSP ($p > 0.05$). More specifically, gender, but not opioid or pain trajectory memberships, was associated with presence/absence of CPSP ($X^2(5) = 13,64$; $p = 0.018$; gender: B = 1.13; standard error = 0.552; Wald = 4.20; $p = 0.040$) and presence/absence of CPSP of moderate to severe intensity ($X^2(5) = 13,85$; $p = 0.017$; gender: B = 1.97; standard error = 0.862; Wald = 5.22; $p = 0.022$) at 6 months. Females were more likely to report CPSP compared to males.

Results of general linear model examining associations between opioid and pain trajectory membership and gender with levels of pain disability at 6 months showed an overall significant effect of gender ($F(1;89) = 4.22$, $p = 0.043$), but not pain or opioid trajectory memberships.

Results of the multivariate general linear model examining associations between pain and opioid trajectories and psychological outcomes at 6 months (pain catastrophizing, anxiety and depression) showed an overall significant effect of opioid trajectory membership (Pillai's Trace = 0.21, $F(9;255) = 2.17$, $p = 0.025$) and gender (Pillai's Trace = 0.11, $F(3;83) = 3.49$, $p = 0.019$) but not pain trajectory membership ($p = 0.297$). More specifically, opioid trajectory membership and gender were significantly associated with levels of pain catastrophizing at 6 months ($p < 0.05$) (see Figure 4 for details).

**Discussion**

This study showed that patients can be grouped into 4 different trajectories in terms of (1) postsurgical pain intensity at movement and (2) cumulative opioid

consumption. Opioid consumption trajectories were significantly associated with pain catastrophizing outcomes at six months.

*Repartition of Patients into the Pain and Opioid Consumption Trajectories*

The results showed that belonging to the lowest opioid consumption trajectory was associated with increased likelihood to be classified in the constant mild pain trajectory. This was not the case necessarily for the higher opioid consumption trajectories; namely patients in the highest opioid consumption trajectory were not systematically classified into the constant moderate pain trajectory. This suggests that the association between pain intensity and opioid consumption goes beyond the pain experience and is multifactorial. While a significant body of literature has found an association between levels of acute post-operative pain intensity and opioid consumption, (Lindberg et al., 2017; Maheshwari et al., 2016) such association has not been found in other studies (Seong Tan et al., 2013) or has been shown to vary with respect to the strength of association based on variables such as age (Gagliese et al., 2008). The association between pain intensity and opioid consumption in the days following surgery might be influenced or mediated by other factors, such as psychological distress or peri-operative factors. Psychological factors have been shown to influence pain intensity reports acutely post-surgically beyond levels of opioid consumption (Bot et al., 2014). Results from this study however showed that anxiety variables were associated with opioid trajectories (baseline anxiety predicted opioid trajectory membership while trajectory membership predicted 6-month pain catastrophizing). No such association was found for pain intensity trajectories; rather baseline depressive symptoms predicted pain

trajectories. This suggests that perhaps pre-operative anxiety might influence pain perception and play a greater role on post-operative behaviors (consumption of opioids).

*Intervention Arm and Trajectory Memberships*

Group assignment (intervention vs. placebo) was surprisingly not predictive of trajectory membership in either model. In the primary clinical trial paper published on these data (Karanicolas et al., in press), results suggested that patients in the ropivacaine group consumed significantly less opioids over a 72-hour period compared to patients in the control group. Taking together, these results suggest that while procedural techniques and drug administration during surgery impact on global amount of opioid consumption, discriminant factors in opioid consumption, namely initial levels and speed of consumption, are important elements of the acute post-surgical experience that have an impact on long-term outcomes. These elements points to the need to better understand trajectories of in-hospital opioid consumption following surgery and risk factors for elevated opioid consumption trajectories as this might propose early intervention strategies to minimize the risks of poor long-term outcomes.

*Acute Pain Trajectories*

Results from the acute pain trajectory model are strikingly similar to those obtained among patients undergoing total hip arthroplasty (Page et al., 2016), namely highlighting subgroups of patients with unchanging elevated or mild pain intensities as well as those with rapidly improving pain intensity. The literature is controversial regarding the association between acute postoperative pain trajectories and CPSP outcomes (Althaus et al., 2014; Bonnet et al., 2012; Page et al., 2016). While acute post-surgical pain, typically measured as a static variable, is a common risk factor for CPSP

(Katz 2012; Katz et al., 1996; Katz and Seltzer 2009; Perkins and Kehlet 2000; Schug and Bruce 2017), the lack of such significant association in pain trajectory studies highlights the importance of examining the heterogeneity of pain responses acutely in the understanding and the prevention of CPSP.

*Opioid Consumption Trajectories*

To our knowledge, this is the first study to examine opioid consumption trajectories acutely following surgery using a latent class model. Results showed that as early as 12-24 hours after surgery differences in amount of opioid consumption can be observed and these differences only increase over time. In other words, results point to the importance of detecting early on elevated opioid consumption as it is most likely to continue to remain elevated over the subsequent days, thus increasing the risk that a patient will transition to prolonged opioid use (Clarke et al., 2014).

*Trajectories and Long-Term Outcomes*

The absence of a significant association between opioid consumption trajectories with six-month pain disability and CPSP might be explained by the complexity of the association between chronic pain, disability and their predictors. Interestingly, opioid consumption trajectories predicted six-month pain catastrophizing, suggesting an association between opioid consumption and psychological responses. As stated previously, in-hospital opioid consumption is multifactorial (Hah et al., 2017; Ip et al., 2009) (such as being influenced by depression, anxiety, catastrophizing, physiological response to opioids, etc.). Results from the current study do not allow us to determine causal mechanisms. But it is possible that targeting opioid consumption along with

influencing psychological factors shortly after surgery might help prevent poor long-term outcomes (Huang et al., 2016; Katz et al., 2015; Weinrib et al., 2017).

Results suggests that from the first 24 hours of opioid consumption after surgery, it is possible to identify patients at risk of poor long-term outcomes (e.g., individuals who have consumed more than 40mg of morphine equivalent dose). Given that most patients are not discharged from hospital until typically at least 2 days later, this provides a window of opportunity for intervention strategies to modify consumption trajectory and minimize the chances of poor outcomes. Such initiative of early postsurgical interventions has been shown to lead to sustained favorable outcomes in terms of long-term opioid consumption months after surgery (Huang et al., 2016; Katz et al., 2015; Weinrib et al., 2017).

*Study Limitations*

This study was limited by only one time point to measure long-term outcomes. Knowing that pain is dynamic, replicating the results with multiple times points measuring acute post-hospital discharge and monthly pain and opioid statuses would allow deeper understanding of the relationship between pain and opioid trajectories and long-term outcomes. The vast majority of patients had primary or secondary metastatic cancer. It is possible that cancer status at six months could have influenced patients' pain reports, yet such variables was not measured.

*Future Studies*

Beyond the need to replicate the opioid consumption trajectory model, the current findings that pain intensity and opioid consumption trajectory memberships do not significantly overlap suggest that perhaps other variables fully mediate whether and how

individuals use opioids to manage their acute postsurgical pain. Failure to take into account these subgroup interactions might in part explain the difficulties to modify acute postoperative factors with the aim of reducing CPSP (Weinrib et al., 2017). It remains to be understood how pre- and peri-operative anxiety might explain some of these associations. Anxiety has typically be identified as an important predictor of CPSP (Burns et al., 2015).

*Conclusions*

This is the first study to examine the association between acute postsurgical pain and opioid consumption trajectories and long-term outcomes. Results showed the importance of examining subgroup differences in the acute postoperative period to predict poor long-term outcome and identify key characteristics that can lead to the development of early interventions that are cost-effective and targeted to high risk individuals.

## Authors contributions

All authors have approved the submitted version of the manuscript.

All authors have made significant contributions to the study conception and design (HC, PK, JK, SC, AW, PM, SM, CS, NC, JH, CL, PG) data acquisition (HC, PK, SC, AW, PM, SL, NA, JS, SM) and/or analysis and data interpretation (HC, GP).

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## Original publication

Portion of this project has been submitted for poster presentation at the Canadian Pain Society Conference in May 2018 and conference proceedings. Results from the original randomized controlled clinical trial have been published (Karanicolas et al. 2018, Annals of Surgery). This manuscript focused on the acute care outcomes associated with MOTAP intervention and the long-term outcomes were not included in that manuscript.

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## Figure Captions

Figure 1. Study flow chart

Figure 2. Amounts of cumulative opioid consumption and pain intensity scores at movement over the first three post-operative days based on allocation (intervention vs. placebo group).

Figure 3. Results of the pain intensity during movement and cumulative opioid consumption trajectories each showing four subgroups that differ in terms of initial levels and rates of change over time.

Figure 4. Results of the multivariate general linear model showing levels of pain catastrophizing (PCS) [left column], depression (Hospital Anxiety Depression Scale (HADS) – Depression) [central column] and anxiety (Hospital Anxiety Depression Scale (HADS-A) [right column] across opioid (top row) and pain at movement (bottom row) trajectories. Results show differences in levels of pain catastrophizing levels (figure A1) at six months across opioid consumption trajectories.

Table 1

Table 1. Baseline and 6-month descriptive statistics for the overall sample as well as based on opioid and pain trajectory membership

| | BASELINE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Opioid Trajectories (n=150)** | | | | **Pain Trajectories (n=148)** | | | | **Overall** |
| | **Traj 1** | **Traj 2** | **Traj 3** | **Traj 4** | **Traj 1** | **Traj 2** | **Traj 3** | **Traj 4** | **sample** |
| | **n=32** | **n=51** | **n=41** | **n=16** | **n=30** | **n=7** | **n=50** | **n=51** | |
| **Age** | 65.71 (10.2) | 62.88 (10.1) | 60.50 (12.5) | 49.87 (13.7) | 64.87 (10.8) | 67.43 (11.0) | 61.22 (11.1) | 58.27 (13.1) | 61.55 (12.0) |
| **Female** (N (%)) | 15 (48.4) | 22 (43.1) | 15 (39.5) | 7 (43.8) | 12 (40.0) | 3 (42.9) | 19 (38.0) | 25 (49.0) | 63 (41.2) |
| **Pain** (N (%)) | 6 (19.4) | 7 (13.7) | 8 (21.1) | 5 (31.3) | 4 (13.3) | 3 (42.9) | 5 (10.0) | 16 (31.4) | 29 (19.0) |
| **Analgesics** (N (%)) | 6 (19.4) | 5 (9.8) | 6 (15.8) | 3 (18.8) | 4 (13.3) | 3 (42.9) | 2 (4.0) | 12 (23.5) | 22 (14.4) |
| **PDI** | 3.27 (9.5) | 3.65 (9.1) | 4.56 (11.9) | 11.86 (17.2) | 1.62 (4.73) | 9.71 (21.5) | 3.04 (8.8) | 9.72 (16.0) | 5.45 (12.5) |
| **PCS** | 9.52 (12.0) | 6.70 (8.2) | 7.53 (12.1) | 12.50 (12.4) | 10.17 (11.6) | 13.71 (12.8) | 7.07 (8.9) | 8.69 (12.5) | 8.28 (11.0) |
| **HADS-A** | 3.90 (3.9) | 4.94 (3.8) | 5.89 (4.2) | 7.44 (3.6) | 4.10 (3.0) | 6.14 (6.1) | 3.81 (3.2) | 7.47 (4.2) | 5.26 (4.1) |
| **HADS-D** | 2.42 (2.6) | 2.86 (2.9) | 3.34 (4.1) | 4.88 (3.8) | 1.90 (2.0) | 3.43 (3.7) | 2.72 (3.0) | 4.29 (4.1) | 3.09 (3.7) |
| | **PERI-OPERATIVELY** | | | | | | | | |
| | **Opioid Trajectories (n=150)** | | | | **Pain Trajectories (n=148)** | | | | **Overall** |
| | **Traj 1** | **Traj 2** | **Traj 3** | **Traj 4** | **Traj 1** | **Traj 2** | **Traj 3** | **Traj 4** | **sample** |
| | **n=32** | **n=51** | **n=41** | **n=16** | **n=30** | **n=7** | **n=50** | **n=51** | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** (N (%)) | | | | | | | | | |
| Ropivacaine | 18 (58.1) | 27 (52.9) | 14 (36.8) | 6 (37.5) | 24 (80.0) | 0 (0.0) | 20 (40.0) | 19 (37.3) | 71 (46.4) |
| **Diagnosis** (N (%)) | | | | | | | | | |
| Primary/metastatic cancer | 30 (96.8) | 50 (98.0) | 36 (94.7) | 15 (93.8) | 29 (96.7) | 7 (100.0) | 48 (96.0) | 49 (96.0) | 148 (96.7) |
| | **6-MONTH FOLLOW-UP** | | | | | | | | |
| | **Opioid Trajectories** | | | | **Pain Trajectories** | | | | **Overall sample** |
| | **Traj 1 n=32** | **Traj 2 n=51** | **Traj 3 n=41** | **Traj 4 n=16** | **Traj 1 n=30** | **Traj 2 n=7** | **Traj 3 n=50** | **Traj 4 n=51** | |
| **CPSP** (N (%)) | 3 (12.5) | 5 (11.6) | 8 (26.7) | 4 (26.7) | 4 (16.0) | 1 (16.7) | 3 (7.1) | 13 (31.0) | 22 (17.5) |
| **CPSP mod/sev** (N (%)) | 1 (4.2) | 3 (7) | 4 (13.3) | 2 (13.3) | 3 (12.0) | 0 (0.0) | 1 (2.4) | 6 (14.3) | 10 (8.0) |
| **NRS-rest** (median; IQR) | 3 (2-6) | 4 (2-5) | 3.5 (2.25-4) | 4.5 (1.75-8.75) | 4.5 (2.5-5) | 4 (4-4) | 3 (1-6) | 3 (2.5-4.5) | 3.5 (2-5) |
| **PDI** | 1.42 (4.3) | 3.68 (8.1) | 6.67 (12.7) | 11.00 (13.4) | 2.57 (7.2) | 10.14 (13.2) | 3.24 (7.6) | 8.03 (13.3) | 5.60 (10.8) |
| **PCS** | 2.67 (3.6) | 4.17 (6.2) | 6.21 (9.5) | 11.83 (14.0) | 4.88 (8.0) | 8.14 (8.0) | 3.18 (5.7) | 7.57 (10.5) | 5.71 (8.9) |
| **HADS-A** | 3.09 (3.3) | 2.95 (3.5) | 4.13 (4.38) | 5.46 (3.9) | 2.46 (3.1) | 4.14 (4.7) | 2.91 (3.4) | 4.81 (4.2) | 3.71 (4.0) |
| **HADS-D** | 1.48 (1.2) | 3.37 (3.1) | 3.29 (3.9) | 5.80 (4.8) | 2.38 (2.7) | 3.14 (2.9) | 2.80 (3.9) | 4.05 (3.6) | 3.16 (3.5) |

*Note : Pain: Number of patients reporting ongoing pain at baseline; Analgesics: Number of patients taking pain medication prior to surgery; PDI : Pain Disability Index; PCS : Pain Catastrophizing Scale; HADS-D : Hospital Anxiety and Depression – Depression subscale; HADS-A : Hospital Anxiety and Depression Scale – Anxiety subscale; CPSP: Chronic Post-Surgical Pain; CPSP mod/sev: CPSP of moderate to severe intensity (≥4/10); NRS: Numeric Rating Scale; IQR: Inter-quartile range*

Table 2. Model fit indicators for the opioid trajectory and pain trajectory models

| Opioid Trajectory Model | | | | |
|---|---|---|---|---|
| Number of trajectories | Linear | | Linear + Quadratic | |
| | AIC | BIC | AIC | BIC |
| 1 | 3930.22 | 3939.26 | 3917.90 | 3929.95 |
| 2 | 3276.27 | 3294.33 | 3236.83 | 3260.92 |
| 3 | 3004.70 | 3031.79 | 2944.50 | 2980.63 |
| 4 | 2792.45 | 2828.58 | 2701.63 | 2749.80 |
| 5 | *2569.52* | *2614.68* | *2439.92* | *2500.14* |
| *6* | *2575.52* | *2629.71* | *2365.89* | *2438.14* |
| *7* | *2463.10* | *2526.32* | *2292.46* | *2376.76* |
| *8* | *2447.23* | *2519.48* | *2266.03* | *2362.37* |
| Pain at Movement - Trajectory Model | | | | |
| Number of trajectories | Linear | | Linear + Quadratic | |
| | AIC | BIC | AIC | BIC |
| 1 | 5549.10 | 5558.07 | 5551.09 | 5563.05 |
| 2 | 5399.85 | 5417.80 | 5400.34 | 5424.27 |
| 3 | 5390.91 | 5417.83 | 5389.20 | 5425.09 |
| 4 | 5373.86 | 5409.75 | 5376.83 | 5424.67 |
| 5 | *5374.18* | *5419.04* | *5379.32* | *5439.13* |
| 6 | *5380.18* | *5434.01* | *5376.63* | *5448.40* |
| 7 | *5384.95* | *5447.75* | *5380.56* | *5464.30* |
| 8 | *5390.95* | *5462.72* | *5386.96* | *5482.65* |

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion
Models in italic are excluded given that the smaller trajectory in each of these models did not contain a minimum of 5% of the sample.

Table 3. Distribution of patients according to opioid and pain trajectory membership

| | | Opioid Trajectories | | | | |
|---|---|---|---|---|---|---|
| | | **Traj 1** | **Traj 2** | **Traj 3** | **Traj 4** | **Total** |
| **Pain Trajectories** | **Traj 1** | 14 | 12 | 3 | 1 | **30** |
| | **Traj 2** | 2 | 2 | 1 | 1 | **6** |
| | **Traj 3** | 11 | 22 | 9 | 7 | **49** |
| | **Traj 4** | 3 | 13 | 25 | 7 | **48** |
| | **Total** | **30** | **49** | **38** | **16** | **133** |

($\chi^2$ (df=9) = 33.36; $p < 0.001$).

*1 patient in pain trajectory 1, 1 patient in pain trajectory 2, 1 patient in pain trajectory 3 and 3 patients in pain trajectory 4 did not have membership in the opioid trajectory because of insufficient opioid data. Similarly, 2 patients in opioid trajectory 1, 2 patients in opioid trajectory 2 and 3 patients in opioid trajectory 3 did not have membership in the pain trajectory because of insufficient pain data.

Figure 1



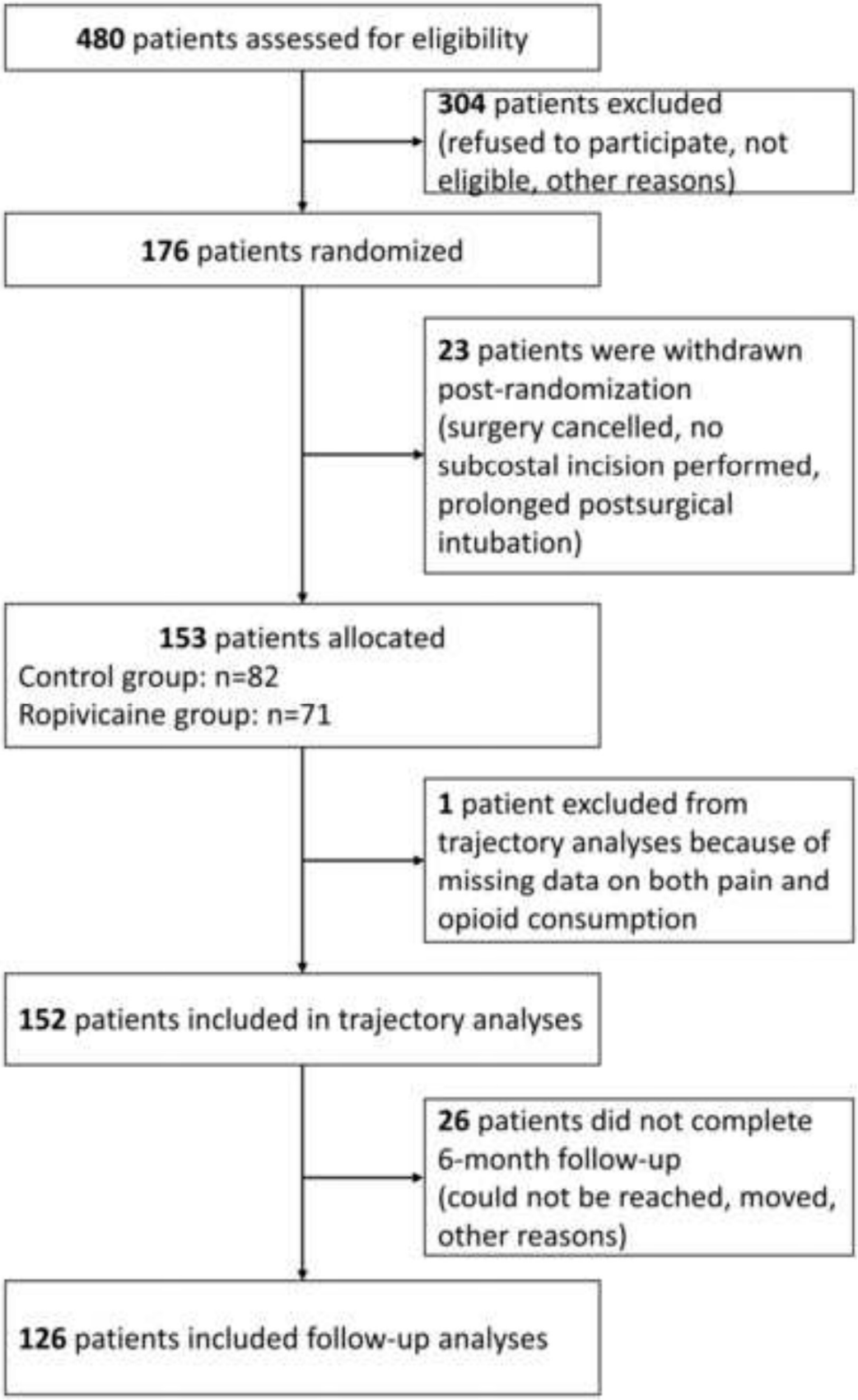
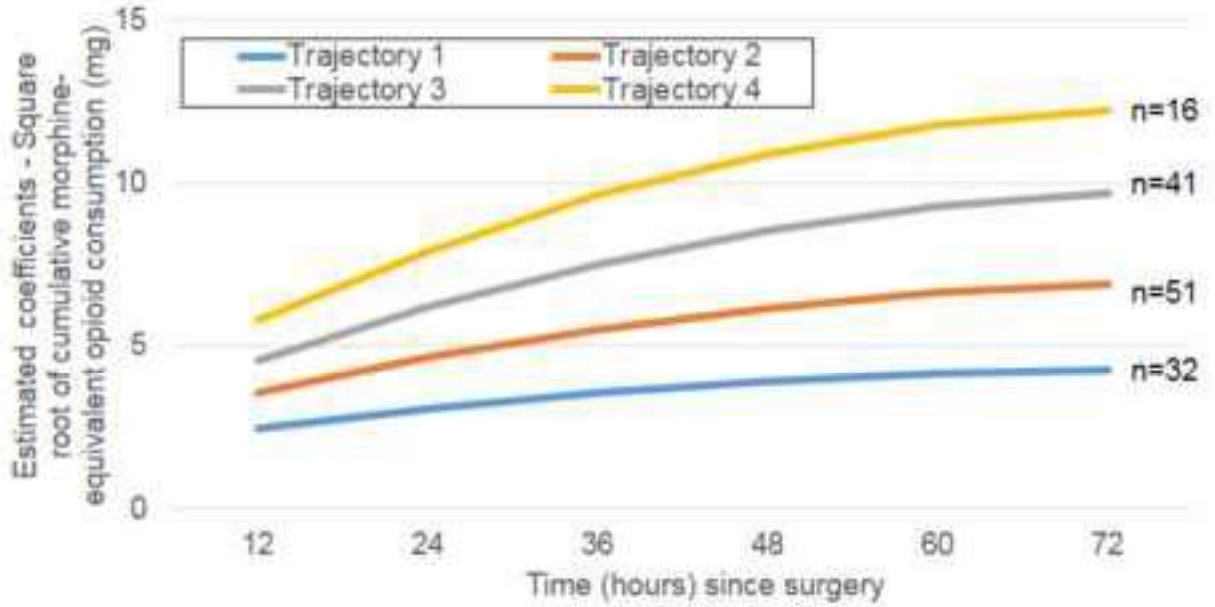


Figure 2

Click here to access/download;Figure;Figure 2. Trajectories_R1.tif



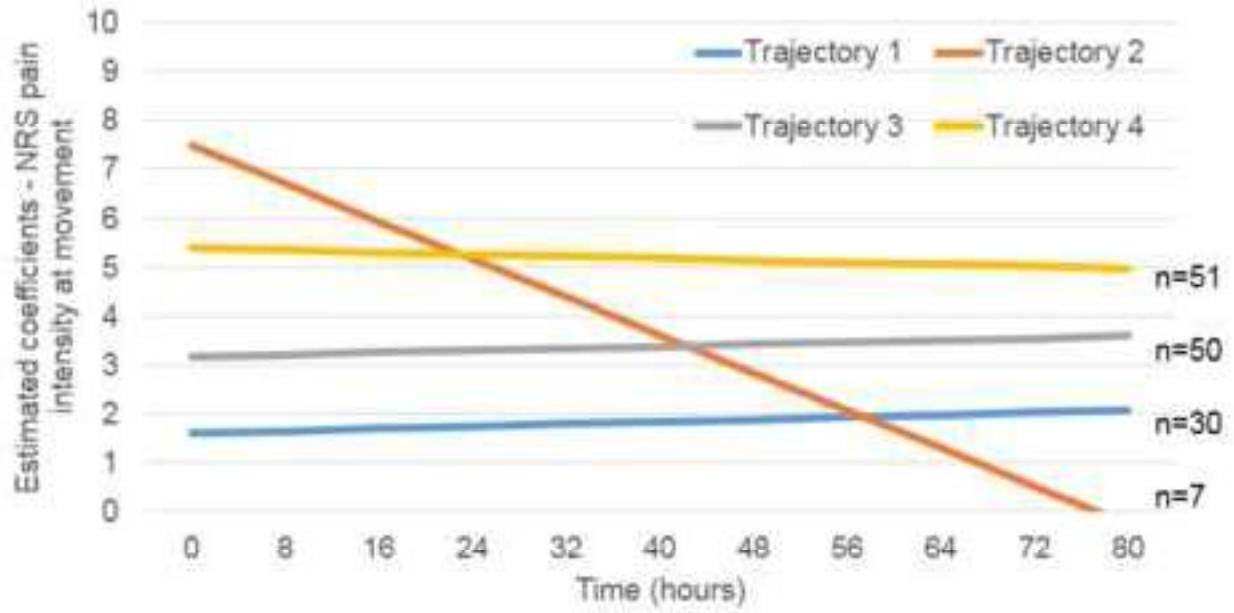
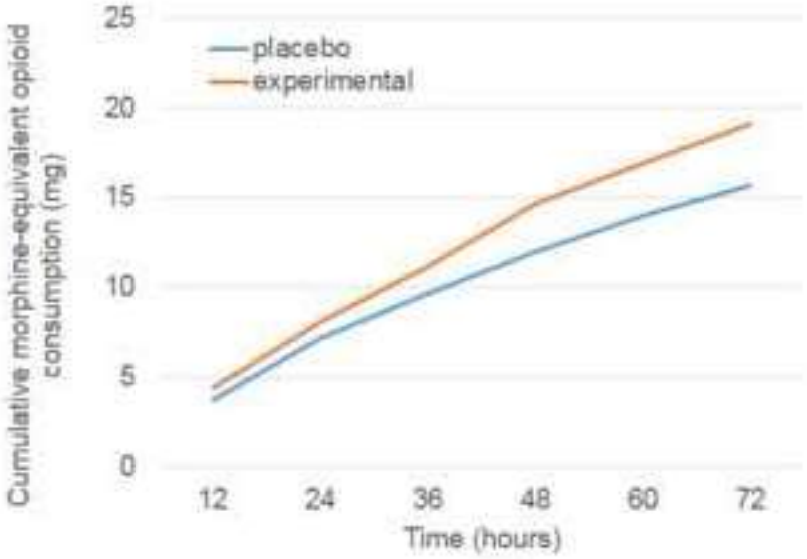



Figure 3





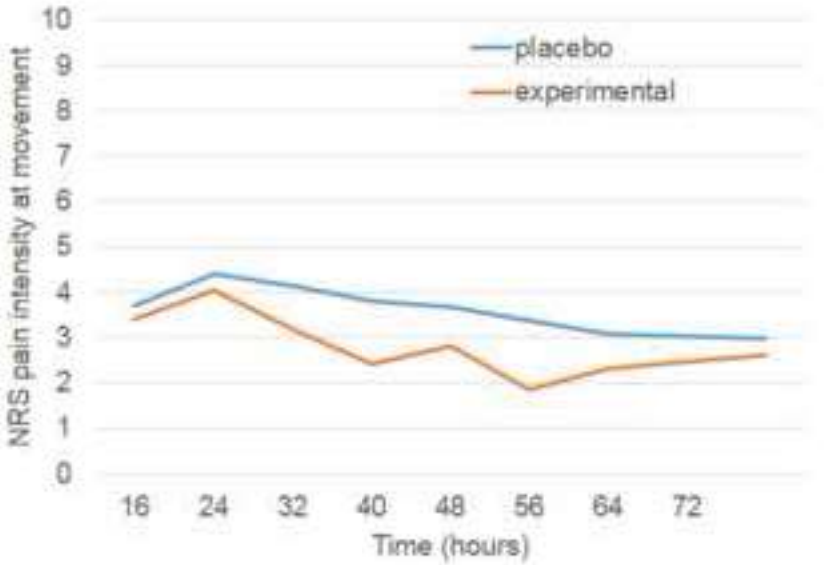



Figure 4