

Affective effects of pre-surgery opioids (AFFECT2): a randomized double-blind placebo-controlled trial

A randomized, double-blind placebo-controlled Phase IV study with three drug arms (three doses each) in healthy adult surgery patients, to investigate the affective short-term effects of morphine, oxycodone, and fentanyl, administered intravenously to the participants before the induction of general anesthesia.

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Compound: morphine «Orion», oxycodone «Hameln», fentanyl «Hameln»

Brief Title: Affective effects of pre-surgery opioids

Study Phase: IV

Acronym: Affect2

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Protocol Amendment Summary of Changes Table

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1. Protocol Summary

1.1. Synopsis

Protocol Title: *Affective effects of opioids on pre-surgery opioids (AFFECT2): a randomized double-blind placebo-controlled trial*

A randomized, double-blind placebo-controlled Phase IV study with three drug arms (three doses each) in healthy adult surgery patients, to investigate the affective short-term effects of morphine, oxycodone, and fentanyl, administered intravenously to the participants before the induction of general anesthesia.

Brief Title: Affective effects of pre-surgery opioids

Rationale:

Opioid medications are commonly used in many fields and aspects of medicine, in particular for the management of surgical and postsurgical pain. In Norwegian hospitals, as a standard procedure for anesthesia, an opioid is usually administered to the patients before the hypnotic used to induce general anesthesia.

While opioid analgesics are known to elicit certain side effects as well as pain relief (Angst et al., 2012), their effects on the patients' subjective emotional (affective) state are less well described. Besides their analgesic effects, opioids are often considered to have beneficial effects on mood (such as relieving anxiety or having anti-depressive effects) (Colasanti, Rabiner, Lingford-Hughes, & Nutt, 2011; Schaffer, Nordahl, Schaffer, & Howe, 2007).

However, results from a quality control study conducted by our team in surgery patients on the operating table, show that the opioid analgesic remifentanyl induced only a weak reduction of anxiety, and the majority of patients reported feeling worse or equally good, but not better, after the infusion.

On the basis of these open-label findings, we will now conduct a more comprehensive, randomised, double-blind placebo-controlled study comparing the affective effects (mood and drug specific effects on a verbal numeric rating scale 0-10, see Table 1) induced by three commonly used opioid analgesics (morphine, oxycodone and fentanyl) or placebo administered before surgery in a clinical setting associated with physiological and psychological acute stress.

To the best of our knowledge, no study has compared the short-term effects of opioids analgesics on emotions, stress response and the sedation level in a clinical (operating theatre) setting.

As a consequence, contributing to the knowledge on the affective reactions to distinct opioid analgesics will provide important information to the clinicians who wish to optimize both pre- and post-surgery treatments and pain management plans.

Table 1 - Objectives and Endpoints:

Objectives	Endpoints	Assessments
Primary		
Describe the subjective effects of morphine “Orion”, oxycodone “Hameln”, and fentanyl “Hameln” (each at three different doses: small, medium, and large), and placebo when administered pre-surgery.	<p>Mean ratings and corresponding 95% confidence intervals for each of the 10 treatment arms for the following 10 self-report items:</p> <p>Pre and post treatment:</p> <ul style="list-style-type: none"> • Anxious • Relaxed • Pain level • Good <p>Post treatment only:</p> <ul style="list-style-type: none"> • Dizzy • Sedated • High • Euphoric • Drug liking • Drug disliking 	<p>Subjective state and acute subjective drug effects rated by the participants on numeric rating scales (0 “not at all” to 10 “very much”) pre and post treatment administration.</p> <p>Primary outcomes are post-drug ratings or change pre to post for items anxious, relaxed, pain level, and good.</p>
Secondary		
Determine the preferred treatment among the three opioids (each at three different doses), and placebo in terms of beneficial effects pre-surgery.	<p>P-scores (ranking metric) based on pairwise differences between all 10 treatments arms in mean ratings post treatment on the following 4 self-report items:</p> <ul style="list-style-type: none"> • Anxious • Relaxed • Pain level • Good 	<p>Subjective state rated by the participants on numeric rating scales (0 “not at all” to 10 “very much”) post treatment administration.</p>

<p>Determine onset time of subjective drug effect of the three opioids (each at three different doses) and proportion of participants that report feeling a drug effect within 0-2 minutes</p>	<p>Proportion of participants in each arm that reports an effect within 0-2 minutes, or responds yes at 2 minutes, or reports feeling a drug high and report dizziness, both ratings ≥ 2.</p> <p>The mean onset time of first drug effect (seconds post-administration) for those who felt an effect</p>	<p>After drug administration, the patient is asked to indicate when they first feel a drug effect, and the time (seconds post-administration) is recorded along with the patient's description of this effect. In the case that no effect has been indicated within the first two minutes, patients are asked if they feel an effect and if so, to describe it.</p>
<p>Replicate previous findings that prior opioid experience and negative affect prior to surgery predict improvements in mood following administration of opioids pre-surgery.</p>	<p>Changes in ratings of feeling good and anxious from pre to post treatment, recoded to an ordinal scale with the three levels "feeling worse" (≥ 1 point decrease), "feeling the same" (no change), and "feeling better" (≥ 1 point increase).</p>	<p>Subjective state rated by the participants on numeric rating scales (0 "not at all" to 10 "very much") pre and post treatment administration.</p>

Exploratory		
Describe the physiological effects of the three opioids (each at three different doses) when administered pre-surgery.	Mean and corresponding 95% confidence intervals for each of the 10 treatment arms for the following 2 physiological measures collected pre and post treatment: <ul style="list-style-type: none"> Heart rate Heart rate variability 	ECG collected from the participants pre and post treatment administration.
Explore whether changes in subjective state from pre to post treatment coincide with changes in physiological state from pre to post treatment when the treatment is administered pre-surgery.	Correlations between numeric changes in physiological measures (heart rate, and heart rate variability) from pre to post treatment and numeric changes in subjective state measures (anxious, relaxed, pain level, and good) from pre to post treatment, plus post-drug 'high' rating.	Subjective state rated by the participants on numeric rating scales (0 "not at all" to 10 "very much") pre and post treatment administration. ECG collected from the participants pre and post treatment administration.

Brief Summary:

Patients in this study will undergo surgery according to standard procedure for anaesthesia, in which an opioid is given before the hypnotic used to induce general anaesthesia. Specific to this study, patients are asked standardized questions about their well-being and affective state before and after the administration of the opioid. Participants will be randomized to receive placebo or one of three opioids commonly used in surgery settings before the induction of general anaesthesia, at one of three equianalgesic doses. The drugs and the placebo will be administered intravenously:

Morphine	Oxycodone	Fentanyl
0.9% NaCl (saline)		
2.5 mg	2.5 mg	0.025 mg
5 mg	5 mg	0.05 mg

10 mg	10 mg	0.1 mg
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The scope of the RCT is limited to the pre-operative analgesic administered on the operating table, and baseline measures recorded on the operating table immediately before. All other anaesthesia and surgery-related procedures will remain unaltered. Administration of medications at any other time, e.g. on the morning of the surgery, during the surgery and after the surgery, will be unaltered. The use of a placebo for one subgroup of the RCT does not represent a deviation from standard clinical care, since many anaesthetists choose not to administer an opioid before anaesthesia. Both outpatients and inpatients will be included in the study.

Based on pilot data and experience from a recent quality control study (Eikemo et al., 2022), we expect to enroll 800-1000 participants in total. See analysis plan.

Note: “Enrolled” means a participant’s agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Participants will be randomized and allocated to ten different groups, receiving either placebo or one of the three study drugs before the start of the induction of general anaesthesia (Figure 1).

The study starts when the participant enters the day surgery unit or the ward and signs the informed consent and ends when the general anaesthesia induction has been conducted. The duration of the study following the administration of the randomized drug is no more than 10 minutes.

Discontinuation from the study:

- Voluntary withdrawal by the participant (withdrawal of written consent).
- Occurrence of a serious event judged by the investigator.

Data Monitoring/Other Committee:

Yes, via Forskningsenheten at Vestre Viken Trust.

1.2. Schema

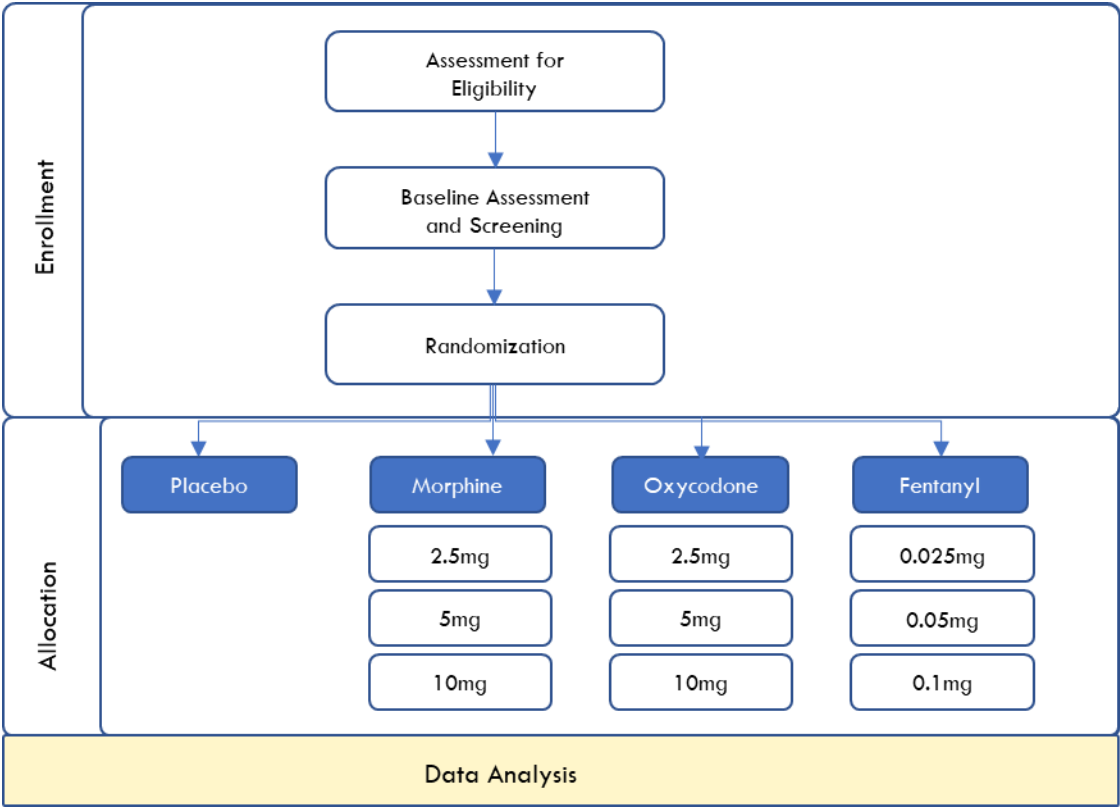


Figure 1 – Flow Chart RCT AFFECT2.

Study Timeline

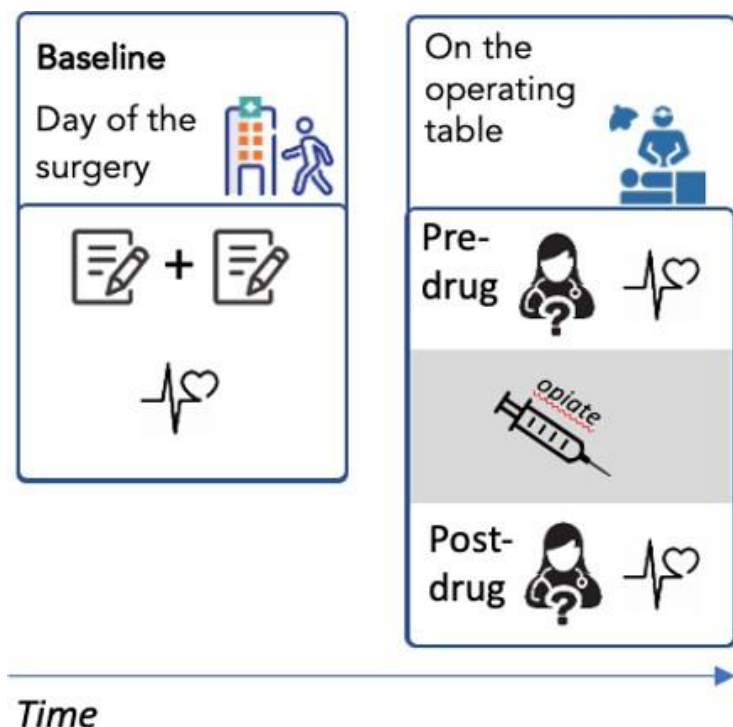


Figure 2. RCT AFFECT timeline.

Baseline before surgery:

After informed consent, the patients fill in a questionnaire with general demographic and health data relevant to surgery (e.g. age, gender, BMI, type of surgery, smoking status).

In addition, we will collect data on pre-operative pain, depression, anxiety (Hospital Anxiety and Depression Scale) and mood.

- **Subjective:** a brief questionnaire on their current affective state, pain (items from Brief Pain Inventory (BPI) and prior opioid use. Affective state items include feeling “good”, “safe”, “anxious”, “upset” and “nervous”.
- **Physiological:** After filling in the questionnaire, baseline heart rate variability will be recorded during a 10min resting period in the waiting room before drug administration. The heart rate equipment will stay in place until the patient is asleep.

On the operating table pre-surgery:

- **Pre:** During the first minutes immediately preceding surgery, we first ask the patient a short series of questions about their affective state, e.g. how “good”, “anxious”, “pain”, and “relaxed” they feel on a numerical rating scale NRS 0-10. We also record heart rate and blood pressure.

- **Drug administration:** Following this, the pre-surgery opioid is administered. In this study, we will use a dose of intravenously morphine (2.5 – 5 – 10 mg), oxycodone (2.5 – 5 – 10 mg) and fentanyl (0.025 – 0.05 – 0.1 mg). In addition, one group receive placebo (saline)
- **Post:** After drug administration, the patient is asked to indicate when they first feel a drug effect, and the time (seconds post-administration) is recorded along with the patient's description of this effect. Next, after a standardized waiting time (2 minutes after the end of drug injection, based on a trade-off of minimum discomfort for the patient and the best opioid analgesic drug effects of morphine, oxycodone and fentanyl), the study personnel ask further questions about the patients' affective state. In the case that no effect has been indicated within the first two minutes, patients are asked if they feel an effect and if so, to describe it. The patient is then asked to report on an NRS 0-10, again how "*good*", "*anxious*", "*pain*", and "*relaxed*" they feel on a numerical rating scale NRS 0-10. We also measure acute drug effects such as "*high*", "*liking the effect*", "*disliking the effect*", "*euphoric*", "*dizzy*", and "*sedated*"; partially selected from the Drug Effects Questionnaire (DEQ27) commonly used to assess abuse liability of drugs. During the RCT data collection we will also record heart rate and heart rate variability (HRV).

A few patients might experience intense anxiety or distress on the operating table; the anaesthesiologist/nurse can make the decision to proceed with the induction of the general anesthesia in such cases, skipping the pre/post drug data collection.

1.3. Schedule of Activities

Procedure	Intervention Period		
	Baseline	On the operating table ~10 minutes before anaesthesia induction	On the operating table ~ immediately before anaesthesia induction
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Medical history (includes substance usage)	X		
Past and current medical conditions	X		
Questionnaires	X		
Heart rate variability (10 minutes)	X		
Heart Rate Variability (~ 5 minutes)		X	X
Vital signs	X	X	X
Randomization (Allocation)	X		
Study intervention (questionnaire before drug/placebo administration)		X	
Study intervention (questionnaire two minutes after drug/placebo administration)			X
SAE review			X

2. Introduction

Despite having fallen under scrutiny for the enormous consequences of the opioid epidemic, opioids medications are still commonly used in many fields and aspects of medicine, in particular for surgical and post-surgical pain. While opioid analgesics are known to elicit variable degrees of side effects and large variability in individual responses (Angst et al., 2012), their effects on the patients' subjective emotional (affective) state are less well described. As a consequence, contributing to the knowledge on the affective reactions to different classes of opioid medications in a real clinical setting, such as surgery, will provide important information to the clinicians to optimize both pre-and post-surgery treatments and pain management plans, and at the same time reducing risks for the patients.

In Norway, about 60% of planned surgery is a day surgery, totalling 216 395 procedures in 2017 (Helsedirektoratet, 2018). The most common outpatient procedures in Norwegian hospitals include minor orthopedic, abdominal, colorectal, gynecological and otorhinolaryngological surgery. The patient group thus spans most of the population, encompassing men and women, young and old, people of low and high socioeconomic status (SES), with and without pain, a history of trauma or other psychosocial vulnerability risk factors. For many patients, these procedures represent their first introduction to opioid drugs, and an unknown proportion of these patients go on to develop opioid misuse.

Opioids analgesics are typically given, before, throughout and after surgery, and patients are often discharged with a prescription for opioids to manage their post-surgical pain at home. Many commonly prescribed opioids are associated with substantial misuse potential, e.g. oxycodone and fentanyl. New clinical data show that the misuse of prescription opioids in chronic pain is driven more by a desire for stress relief than by pain itself (McHugh et al., 2016). These findings fit with epidemiological studies highlighting stress as a vulnerability factor (Stone, Becker, Huber, & Catalano, 2012b). Surgery represents a major stressor at both the physiological and psychological level, and pre-surgery stress relief is cited as one benefit of pre-anaesthesia opioid administration (Doleman et al., 2018).

Besides analgesic effects, opioids are often considered to have beneficial effects on mood (such as relieving anxiety or having anti-depressive effects) (Colasanti et al., 2011; Schaffer et al., 2007). However, preliminary results from a pilot study conducted by our team on the operating table in surgery patients, show that opioid analgesic remifentanyl induced only a weak reduction of anxiety, and the majority of patients reported feeling worse or equally good, but not better, after the infusion. On the basis of these intriguing, preliminary findings, we will now conduct a more comprehensive randomized double-blind placebo-controlled study comparing different classes of opioid analgesic and their effect on affective states.

Opioids analgesics can be administered through a variety of drug formulations. Although most of the opioids commonly used in analgesia have the common feature of acting on the mu-opioid receptor as primary target, large difference between classes of opioids are often seen in clinical practice. Indeed, opioids differ markedly in their side effects (Drewes et al., 2013). Some patients, for example, appear to respond to certain opioids but are intolerant to others, and switching from one class of opioid to another often results in an improvement of symptoms

(Dale, Moksnes, & Kaasa, 2011). These clinical observations have led the pain research on focusing in particular on physical side effects, and less attention has been given to the affective reactions to different classes of opioid medications.

Morphine, oxycodone and fentanyl are three commonly used opioid compounds which differ in chemical structure and pharmacokinetics but share the common mechanism of acting on the mu-opioid system and are all commonly used in clinical practice in Norway. To the best of our knowledge, ours will be the first randomized placebo-controlled study to investigate the affective reactions to opioids medications given in an ecological situation of acute stress such as surgery.

Much of the current knowledge on opioid drug effects – including opioid abuse liability – derives from laboratory studies where healthy people are told they can get an active drug or placebo and that the (experimental) pain stimuli are temporary and unlikely to cause harm. The experimental setting lacks ecological validity and may not generalise to patients undergoing complex surgical treatment with take-home opioid drugs. For instance, acute experimental pain differs from clinical pain mechanisms (Tracey, Woolf, & Andrews, 2019), where there is real tissue damage and uncertainty about when the pain will subside. Moreover, surgery represents a major stressor that deeply impacts the systemic stress response at both physiological and psychological level.

It has been shown that opioid analgesics reduce stress responses such as cortisol release (Bershad, Miller, Norman, & de Wit, 2018), and reducing pre-surgery stress is considered to be one benefit of pre-anaesthesia opioid administration (Doleman et al., 2018). Although there is little research to support such a benefit, administering an opioid a few minutes before anaesthesia in order to manage the patient's stress and to improve postoperative pain is common practice in many hospitals in Norway and internationally (Doleman et al., 2018).

New clinical data examining the contribution of pain and psychological factors in opioid misuse behaviour shows that prescription opioid misuse in pain patients is driven more by a desire for stress relief than by pain itself (Martel, Dolman, Edwards, Jamison, & Wasan, 2014; McHugh et al., 2016). Similarly, high-stress conditions (low socioeconomic status, a history of trauma, symptoms of depression or anxiety and poor social support) are all reported to increase the vulnerability to adverse post-surgery outcomes (Stone, Becker, Huber, & Catalano, 2012a) and risk of opioids misuse. Stress typically increases inflammatory and immune responses, which are heightened in people with anxiety (Stone et al., 2012b), depression (Bjerkeset, Romild, Smith, & Hveem, 2011; Naude, Roest, Stein, de Jonge, & Doornbos, 2018) and a history of trauma (Deighton, Neville, Pusch, & Dobson, 2018). High stress reactivity and reduced ability to regulate negative emotional states could thus be key predisposing risk factors of postoperative adverse events. The biological mechanisms that link psychosocial factors with these health vulnerabilities are still unclear (Garland, Froeliger, Zeidan, Partin, & Howard, 2013). Indeed, stress-related measures such as autonomic markers (e.g. heart rate variability; (Sgoifo, Carnevali, Alfonso Mde, & Amore, 2015; Thomas & Garland, 2017) are emerging as potential predictors and could provide the missing link between psychosocial vulnerability and physical health.

In this study, we will assess and compare the affective effects of three commonly used opioid analgesics (morphine, oxycodone, and fentanyl) administered before surgery in a clinical setting associated with physiological and psychological stress.

2.1. Study Rationale

The aim of the present study is to assess and compare, with a randomized, double-blind placebo-controlled trial, the affective effects of three commonly used opioid analgesics (Morphine «Orion», oxycodone «Hameln» and fentanyl «Hameln») administered in three different doses before surgery in a clinical setting associated with physiological and psychological stress.

2.2. Background

As a starting point, we have conducted an observational quality control study on peri-operative opioid pain management in day surgery patients.

Quality control study – a pilot study

In this observational quality control study, we measured acute effects of the opioid agonist Remifentanyl (effect site concentration 5ng/ml, Minto model) in day surgery patients on the operating table at Kongsberg hospital. Patients rated their levels of “feeling good” and “anxious” on an 0-10 numerical rating scale (NRS) immediately before and 1 minute after receiving remifentanyl infusion. They also rated drug-specific effects such as “feeling high”, “liking the drug effects” and their “level of drug-related discomfort”. Moreover, we collected data on postoperative opioid use and pain during recovery through a telephone interview on the day following the surgery. The study was conducted with the usual standard hospital treatment and as such, did not interfere with the patients’ medical procedures. All the procedures were approved by the data protection officer at Kongsberg Hospital, and all included patients signed informed consent on the day of surgery.

Figure 3 gives an overview of the study procedure and Table 3 of the study sample characteristics.

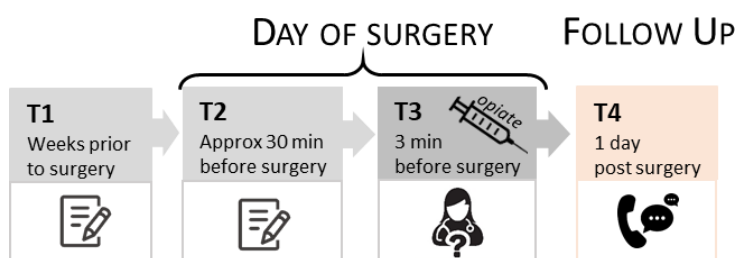


Figure 3. Study timeline of the pilot quality control study. In the weeks prior to surgery (T1) participants received a questionnaire to assess their pain levels, nervousness and demographics as part of the hospital’s standard procedure. On the day of surgery, approximately 30 min before surgery (T2) patients were asked to fill in questionnaires to assess mood, pain and prior opioid use. One minute before and one minute after opioid (administration) (T3), the patient was asked to rate mood, anxiety, drug liking and drug related discomfort. On the day following surgery patients were contacted by phone to assess their mood, pain and pain interference, as well as their pain relief strategies in the last 24h (e.g. use of provided analgesics).

Table 3. Overview of the sample characteristics of the first 160 patients included in the pilot quality control study. Unless otherwise noted, we list mean and standard deviation (SD).

N	160 (96 women)
Age	46.5 years (14.2)
Height	173m (0.1)
Weight	80.3kg (15.5)
Tobacco use	34 (21.3%)
Prior opioid use	103 (64.4%)
Prior pain (weeks before surgery)	73 (45.6%)
<i>Procedure (N)</i>	
Surgical	74
Orthopedic	25
Gynecological	52
Otorhinolaryngological	4

The results of the pilot study show that patients report a clear feeling of ‘drug high’ after remifentanyl infusion. Surprisingly, however, the opioid analgesic induced only a weak reduction of anxiety, and the majority of patients reported feeling worse or equally good, but not better, after the infusion. In the postoperative phone interview, many patients tell us they have not used any of the opioid drugs prescribed for at-home pain relief during the first 24 hours are recovering at home. Stated reasons include a fear of addiction, as well as a wish to keep the analgesics in case of breakthrough/peak pain at a later stage. These preliminary results do not support the opioid pre-induction procedure as an effective manner to produce pre-surgery stress relief. It might be possible that the subjective perception of stress relief does not match the physiological relief reaction to stress.

On the basis of these intriguing, preliminary findings, we will now conduct a more comprehensive randomized double-blind controlled study comparing different classes of pre-surgical opioid analgesics on the subjective and physiological affective reactions in an acute stress clinical situation in Norway.

Possible participants of the AFFECT2 RCT will also be asked if they wish to join a parallel longitudinal study conducted in collaboration with the University of Oslo (UiO) in which we will collect and analyse data on relevant pre-surgery risk factors for problematic opioid use, and to quantify opioid-induced analgesia before and after surgery using prescription registry data.

2.3. Benefit/Risk Assessment

The induction of anaesthesia is defined as the transition from an awake state to an anaesthetized state (Astuto & Lauretta, 2009). In most circumstances, the airway has to be secured with eg. a laryngeal mask or by intubation. Induction of anaesthesia is usually achieved with an intravenous anaesthetic agent of choice, in our clinic mostly propofol, combined with an opioid and (in case of intubation) a nondepolarizing muscle relaxant. While propofol is used to get the patient asleep, the role of the opioid is to prevent the hypertensive response to laryngoscopy or the

handling of the airway and to block the nociceptive response when surgery is initiated. In case of a rather short day surgery operations, a long-acting opioid also contributes to postoperative analgesia. All the drugs used for this randomized clinical trial (oxycodone, morphine, fentanyl) are strong opioids which are used daily in operating theatres. Fentanyl is frequently used before induction, whereas oxycodone and morphine are more frequently used to relieve postoperative pain. The relative (analgesic) potency of opioids can be estimated based on the scientific literature and is described in dose equivalents of morphine (Natusch, 2012). In this study, we will use an equianalgesic dose of intravenously morphine (2.5 – 5 – 10 mg), oxycodone (2.5 – 5 – 10 mg) and fentanyl (0.025 – 0.05 – 0.1 mg). In addition, one group receive placebo (saline). The largest dose is a standard dosage for opioids given prior before anaesthesia inductions.

2.3.1. Risk Assessment

The participant could have received an opioid in a similar equianalgesic dosage prior to the induction of anaesthesia independently of the randomized clinical trial, depending on the preferences of the individual anaesthetist. Compared to the standard pre-surgery procedure, the main difference in the present trial is represented by the administration of three different class of opioids analgesic, all of which have been largely used in clinical setting for several decades. Morphine has been on the market since 1827 (Courtwright, 2001; Inglis, 2018), fentanyl was approved in 1968 (Stanley, 1992), and oxycodone, although already introduced in 1916 (Sneader, 2005), was then reintroduced in 1996 (Inglis, 2018). Opioid analgesics generally have similar adverse effects. Individual differences may exist due to individual genetic and epigenetic differences, e.g. in the composition of opioid receptors, their expression and intracellular signaling mechanisms. In clinical practice, it is not possible to predict exactly how a patient will respond to a given dose of an opioid drug (Angst et al., 2012), and dose titration is usually based on observation of the patient's response. Common adverse effects can include respiratory depression, nausea, low blood pressure, and sedation, beyond others, and the incidence rate of the adverse effects of the three compounds is comparable. Patients are routinely monitored (blood pressure, ECG, oxygen saturation in the blood) and an anaesthetist and an anaesthetist nurse, experienced to handle adverse effects or any airway, respiratory or circulatory problems are on stand-by. At the study sites (Kongsberg, Oslo University Hospital) the responsible anaesthetists are specialists with more than 10 years' experience. Postoperatively, as all hospitals in Norway, the study sites have an established routine to follow-up patients, to identify early potential adverse effects and to handle them, following the Norwegian Standard for Anaesthesia¹.

The only major risk is an anaphylactic reaction or shock due to the specific opioid. These allergies are rare and possible participants with known allergies to any opioid will be excluded. The application of the opioids occurs in an operation theatre with three health professionals (the anaesthetist, the anaesthetist nurse, and the study nurse or study physician) experienced in

¹ <https://www.nafweb.com/dokumenter/norsk-standard-for-anestesi-2016.pdf>

managing any potential life-threatening events. All necessary equipment is available in the surgery setting. In addition, an extra emergency team consisting of two physicians, two specialist nurses, and additional staff is available within three minutes. The participants are in overall good health and they are fasting. All local and national standard operating procedures regarding anaesthesia are followed. At Kongsberg hospital, according to the safety records, no serious anaphylactic shock based on opioids has occurred in the last 20 years. In case of very rare adverse effects (e.g. allergies, which occur in less than 2% of patients (Li, Ue, Wagner, Rutkowski, & Rutkowski, 2017), the clinical staff can unblind the drug at once. Most, if not all, adverse effects of opioids receive the same treatment independently of the class of opioid. We regard therefore, the risk for serious adverse effects as extremely low and the risk of adverse effects which can occur due to the trial (compared to standard treatment) also as extremely low.

Regarding the use of placebo in one treatment arm, the practice of administering intravenous opioid before induction of anaesthesia is highly variable in Norway. The rationale for administering before sleep is preparing for intubation/surgery which is painful and/or make the patient more relaxed before sleep. On the other hand, some patients will feel dizziness and/or itching after intravenous opioid before anaesthesia induction. These side effects are often experienced as unpleasant. Therefore, some anaesthesiologists prefer not to administer opioid before sleep (as in our placebo group). There is no clear evidence of what practice is best. Our study will give a clearer picture of what practice is best: low or high dose of opioid? Or no opioid at all before induction of anaesthesia. All patients in the study will receive an opioid at latest after sleep induction.

2.3.2. Benefit Assessment

The individual participant will not have direct benefits from being enrolled in the investigation, beyond contributing to the knowledge of opioids which might be relevant for the individual at a later time point. This project will help determine which opioid has a relevant impact on how patients feel, especially regarding anxiety and physiological stress, and thus should be preferred to manage stress and anxiety in clinical settings such as pre and post-surgery treatment and palliative care. This knowledge will enable a benefit for future patients.

2.3.3. Overall Benefit: Risk Conclusion

Summarized, opioid administration before anaesthesia induction is part of the standard surgical procedure in many hospitals in Norway. Patients participating in the study will receive a commonly used opioid in similar doses; however, both the patient and the anaesthetic staff will be blinded to the specific type of the opioid drug. A high safety standard, established knowledge of the drugs, highly skilled personnel with more than 10 years of expertise, as well as, and the immediate possibility to unblind the treatment and to implement established methods to treat possible complications, make it highly unlikely that any fatal outcomes or even disadvantages for the participants will occur.

3. Objectives and [Endpoints and/or Estimands]

Objectives	Endpoints	Assessments														
Primary																
Describe the subjective effects of morphine “Orion”, oxycodone “Hameln”, and fentanyl “Hameln” (each at three different doses: small, medium, and large), and placebo when administered pre-surgery.	<p>Mean ratings and corresponding 95% confidence intervals for each of the 10 treatment arms for the following 10 self-report items:</p> <table><tr><td>Pre and post treatment:</td><td>Post treatment only:</td></tr><tr><td>• Anxious</td><td>• Dizzy</td></tr><tr><td>• Relaxed</td><td>• Sedated</td></tr><tr><td>• Pain level</td><td>• High</td></tr><tr><td>• Good</td><td>• Euphoric</td></tr><tr><td></td><td>• Drug liking</td></tr><tr><td></td><td>• Drug disliking</td></tr></table>	Pre and post treatment:	Post treatment only:	• Anxious	• Dizzy	• Relaxed	• Sedated	• Pain level	• High	• Good	• Euphoric		• Drug liking		• Drug disliking	<p>Subjective state and acute subjective drug effects rated by the participants on numeric rating scales (0 “not at all” to 10 “very much”) pre and post treatment administration.</p> <p>Primary outcomes are post-drug ratings or change pre to post for items anxious, relaxed, pain level, and good.</p>
Pre and post treatment:	Post treatment only:															
• Anxious	• Dizzy															
• Relaxed	• Sedated															
• Pain level	• High															
• Good	• Euphoric															
	• Drug liking															
	• Drug disliking															
Secondary																
Determine the preferred treatment among the three opioids (each at three different doses), and placebo in terms of beneficial effects pre-surgery.	<p>P-scores (ranking metric) based on pairwise differences between all 10 treatments arms in mean ratings post treatment on the following 4 self-report items:</p> <ul style="list-style-type: none">• Anxious• Relaxed• Pain level• Good	<p>Subjective state rated by the participants on numeric rating scales (0 “not at all” to 10 “very much”) post treatment administration.</p>														

Determine onset time of subjective drug effect of the three opioids (each at three different doses) and proportion of participants that report feeling a drug effect within 0-2 minutes	<p>Proportion of participants in each arm that reports an effect within 0-2 minutes, or responds yes at 2 minutes, or reports feeling a drug high and report dizziness, both ratings ≥ 2.</p> <p>The mean onset time of first drug effect (seconds post-administration) for those who felt an effect</p>	After drug administration, the patient is asked to indicate when they first feel a drug effect, and the time (seconds post-administration) is recorded along with the patient's description of this effect. In the case that no effect has been indicated within the first two minutes, patients are asked if they feel an effect and if so, to describe it.
Replicate previous findings that prior opioid experience and negative affect prior to surgery predict improvements in mood following administration of opioids pre-surgery.	Changes in ratings of feeling good and anxious from pre to post treatment, recoded to an ordinal scale with the three levels "feeling worse" (≥ 1 point decrease), "feeling the same" (no change), and "feeling better" (≥ 1 point increase).	Subjective state rated by the participants on numeric rating scales (0 "not at all" to 10 "very much") pre and post treatment administration.

Exploratory		
Describe the physiological effects of the three opioids (each at three different doses) when administered pre-surgery.	Mean and corresponding 95% confidence intervals for each of the 10 treatment arms for the following 2 physiological measures collected pre and post treatment: <ul style="list-style-type: none"> Heart rate Heart rate variability 	ECG collected from the participants pre and post treatment administration.
Explore whether changes in subjective state from pre to post treatment coincide with changes in physiological state from pre to post treatment when the treatment is administered pre-surgery.	Correlations between numeric changes in physiological measures (heart rate, and heart rate variability) from pre to post treatment and numeric changes in subjective state measures (anxious, relaxed, pain level, and good) from pre to post treatment, plus post-drug 'high' rating.	Subjective state rated by the participants on numeric rating scales (0 "not at all" to 10 "very much") pre and post treatment administration. ECG collected from the participants pre and post treatment administration.

4. Study Design

4.1. Overall Design

Patient enrolment is planned for end of 2022, and the study will be conducted until 1000 participants are included or until December 2025. The main study centre is Kongsberg Hospital, with additional sites at Oslo University Hospital.

- Randomized double-blind study with ten arms
- Placebo-controlled
- Patients scheduled for surgery will be recruited at the outpatient clinic at Kongsberg and Oslo University Hospital. Patient groups with severe disease burden or other risks will not be enrolled. Consequently, the patients included in this sample are relatively healthy individuals.
- Randomization sequences will be generated prior to the first enrolment by a statistician not affiliated with the present study at UiO (Kongsberg) and by the Clinical Trials Unit at Oslo University Hospital (OUS sites).
- The assignment will be performed by study personnel after the participant has signed the consent form, on the day of the surgery
- Participants will be asked to fill in questionnaires before and on the day of surgery. The total duration of the study after the administration of the randomized drug is approximately 10 minutes.
- Participant will be invited to take part in an observational long-term follow-up study independently of the participation in the AFFECT2 RCT.

4.2. Scientific Rationale for Study Design

The main endpoints of this study are the affective effects of three different opioids administered pre-surgery.

The study will be conducted as a double-blind placebo-controlled randomized design since it is essential that the anaesthesia staff remains blinded to the drug type until completion of the study. Effects of the opioids on patients' affective state are highly relevant in clinical practice. To our knowledge, no study has investigated the effects of opioids medications on emotions, stress response and the sedation level in pre-surgery setting. We have chosen endpoints to yield maximally useful information in the shortest amount of time so that participants will not wait long on the operating table before anaesthesia. Questions on mood are primarily asked pre- and post-drug administration, to assess how each opioid may shape how “good”, “relaxed”, “anxious”, and “pain” participants feel. In addition, 2-4 minutes after drug administration we include key questions on drug effects from the Drug Effects Questionnaire (DEQ), commonly used to assess abuse liability of drugs (Evans, Foltin, Levin, & Fischman, 1995; Morean et al., 2013), such as “drug high”, “liking of drug effects” and “disliking of drug effects”. We also specifically measure drug-induced *euphoria*, *dizziness* and *sedation*.

In combination, these items will allow us to establish a distinct affective effect profile for morphine, oxycodone and fentanyl in the pre-surgery setting. We hope that these results will help determine future treatments, e.g.: which opioid should a clinician preferably use in patients with high anxiety; or which opioid should be used if a patient would benefit from a sedating effect?

This investigation will include a representative group of adult day-surgery and inpatients, which enables us to generalize to a broader population.

4.2.1. Participant Input into Design

The research group at Kongsberg hospital has established a user panel for research questions. The panel members contribute to developing relevant research questions, establishing study designs, give advice for participant recruitments, discuss results and give advice for the implementation of results and information to the public. For the current project, one member of the panel has agreed to participate also in the project group. We also collaborate with the user council of the Vestre Viken health trust. The current proposal was created based on our experiences from conducting a quality control study, including post-surgery phone interviews with day surgery patients at Kongsberg hospital (160 patients). The knowledge arising from these semi-structured conversations with patients, as well as our clinical interactions in the hospital, has informed several aspects of the study design, such as the importance of prior beliefs and attitudes about opioid medications and addiction.

4.3. Justification for Dose

The dosage of opioids given prior to anaesthesia induction varies between 10 mg and 30 mg morphine equivalent (Choudhary et al., 2019; Dutta et al., 2018), or even higher (Wang, Hermann, & Westrin, 1996). The chosen opioid doses for this study represents a normal dose used in these patients' groups, as well as two lower doses per drug to produce a dose-response function. The main function of the pre-induction opioid, when used, is to avoid stress reactions by maintaining the airway with intubation or laryngeal mask. All surgeries conducted in the study group will provoke little to moderate nociception during operation, higher doses would not be used normally to induce anaesthesia. After the induction, the anaesthesia will be continued with a steady-state dose of propofol and remifentanyl, which will be continually adapted according to the observed physiological parameters of the patient. After the induction, when the anaesthesia team will be unblinded, they will be aware whether the patient has received a rather long-acting opioid (Oxycodone «Hameln» or morphine «Orion»), short-acting one (fentanyl «Hameln») or placebo, so that they can adapt the anaesthesia accordingly. The highest dose is estimated as effective in patients with an BMI between 18 and 35.

4.4. End of Study Definition

The end of the study is defined as the end of the anaesthesia induction on the same day.

A participant is considered to have completed the study if he/she has completed all phases of the study, including the interview at pre and post drug just before falling asleep.

5. Study Population

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age:

1. Participants must be 18 years of age or above at the time of signing the informed consent.

Type of Participant and Disease Characteristics:

2. Health status ASA1 or ASA2 as categorised by a medical doctor at the hospital based on medical history, physical examination, laboratory test etc. unrelated to the current study. The American Society of Anesthesiologists physical status (ASA-PS) ASA1 and ASA2 (ASA1 is defined as “Healthy, non-smoking, no or minimal alcohol use” and ASA2 is defined as “Mild diseases only without substantive functional limitations). Being eligible for day surgery means participants are overtly healthy as determined by clinical staff.
3. The participant is considered as eligible for the use of fentanyl, morphine and oxycodone by a medical doctor at the hospital, based on an overall assessment of the psychiatric and somatic condition, used medical drugs, regarding possible interactions and contraindications for the use of the study medicaments.

Weight:

4. Body weight and body mass index (BMI) within the range 18-35 kg/m² (inclusive).

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other criteria:

6. Having good verbal communication skills in Norwegian.
7. Patients undergoing surgery in general anaesthesia:
 - a. Planned day surgery: Orthopedic, minor gastrointestinal surgery, gynecological, hand and foot surgery, and minor vascular procedures.

OR

Inpatients undergoing planned gynecological, minor gastrointestinal, orthopedic surgery or other related procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Known allergic reactions to morphine, oxycodone, or fentanyl. Known allergic reactions to any of the ingredients described in the SPC, pt 6.1.
2. Severe chronic obstructive lung disease,
3. Cor pulmonale,
4. Severe bronchial asthma,
5. Severe respiratory failure with hypoxemia and hypercapnia
6. Moderate to severe hepatic impairment,
7. Moderate to severe kidney failure
8. Acute abdomen
9. Increased brain pressure
10. Head trauma
11. Use of MAO blockers in the last two weeks
12. Hypovolemia
13. Hypotension
14. Myasthenia gravis
15. Any other health status not corresponding to ASA1 or ASA2. This includes patients with severe disease burden, major psychiatric disorders that could interfere with the procedures and communication.
16. Pregnancy. Women of childbearing potential defined as all premenopausal female (a postmenopausal state is defined as no menses for 12 months without an alternative medical cause) will be asked if they are pregnant.
17. Breastfeeding women.
18. Prior or ongoing use of illicit drugs like opioids, cocaine and amphetamine.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

All the patients included in the AFFECT2 RCT will follow the Standard Operating Procedures already in place for at Kongsberg Hospital for all the surgery. Which include:

1. Refrain from consumption of food six hours before the induction of anaesthesia.
2. Refrain from beverages two hours before the induction of anaesthesia

5.3.2. Caffeine, Alcohol, and Tobacco

1. No restrictions beyond 5.3.1

5.3.3. Activity

1. No restrictions beyond the usual preoperative recommendations.

5.4. Screen Failures

Not applicable

5.5. Criteria for Temporarily Delaying

Not applicable

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	[1]	[2]	[3]
Intervention Name	Morphine «Orion»	Oxycodone «Hameln»	Fentanyl «Hameln»
Type	Drug	Drug	Drug
Dose Formulation	Ampule	Ampule	Ampule
Unit Dose Strength(s)	Placebo 0.9% saline		
	2.5 mg	2.5 mg	0.025 mg
	5 mg	5 mg	0.05 mg
	10 mg	10 mg	0.1 mg
Dosage Level(s)	1 single dose	1 single dose	1 single dose
Route of Administration	IV injection	IV injection	IV injection
Use	experimental and active comparator	experimental and active comparator	experimental and active comparator
Investigation Medicinal Product	IMP	IMP	IMP
Sourcing	Provided locally by the trial site	Provided locally by the trial site	Provided locally by the trial site
Packaging and Labeling	Study Intervention will be provided in a syringe labeled with	Study Intervention will be provided in a syringe	Study Intervention will be provided in a syringe

	the participant number	labeled with the participant number	labeled with the participant number
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6.1.1. Medical Devices

ECG monitoring (HRV monitoring pre and post opioid administration)

6.2. Preparation/Handling/Storage/Accountability

1. Only participants enrolled in the study will receive study intervention, and only authorized site staff will supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
2. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
3. Study drugs will be prepared by qualified medical personnel according to the randomization protocol at day of the inclusion of the individual participant. The different study drugs will be matched visually (e.g. colour) during preparation to ensure full blinding. The study drug will be handed out in a syringe labeled with the participant number and date in a syringe:
 - a) Morphine «Orion» will be diluted to 1 mg/ml
 $= 2.5 \text{ mg} = 2.5 \text{ ml} + 7.5 \text{ ml saline} = 10 \text{ ml in a 10 ml syringe}$
 $= 5 \text{ mg} = 5 \text{ ml} + 5 \text{ ml saline} = 10 \text{ ml in a 10ml syringe}$
 $= 10 \text{ mg} = 10 \text{ ml} = 10 \text{ ml in a 10 ml syringe}$
 - b) Oxycodone «Hameln» will be diluted to 1 mg/ml
 $= 2.5 \text{ mg} = 2.5 \text{ ml} + 7.5 \text{ ml saline} = 10 \text{ ml in a 10 ml syringe}$
 $= 5 \text{ mg} = 5 \text{ ml} + 5 \text{ ml saline} = 10 \text{ ml in a 10 ml syringe}$
 $= 10 \text{ mg} = 10 \text{ ml} = 10 \text{ ml in a 10 ml syringe}$
 - c) Fentanyl «Hameln» will be diluted to 0.05mg/ml
 $= 0.025 \text{ mg} = 0.5 \text{ ml} + 9.5 \text{ ml saline} = 10 \text{ ml in a 10 ml syringe}$
 $= 0.05 \text{ mg} = 1 \text{ ml} + 9 \text{ ml saline} = 10 \text{ ml in a 10 ml syringe}$
 $= 0.1 \text{ mg} = 2 \text{ ml} + 8 \text{ ml saline} = 10 \text{ ml in a 10 ml syringe}$
 - d) Natriumklorid 9 mg/ml (saline-placebo) = 10 ml syringe

6.3. Measures to Minimize Bias: Randomization and Blinding

Table 3. – Randomization plan

Generation of the Randomization list	<p><i>The randomization list for Kongsberg will be generated by an independent statistician of the University of Oslo, not affiliated with this study, and stored on TSD.</i></p> <p><i>Other researchers at UiO who are not involved in the RCT data collection will note the results of the allocation sequence and will use opaque, sealed, and sequentially numbered envelopes for its concealment.</i></p> <p><i>Participant's assignment in sealed, opaque envelopes will be only opened for each participant after the study staff obtained consent form and confirmed eligibility on the day of the surgery at Kongsberg Hospital.</i></p> <p><i>At Oslo University Hospital (OUS) an independent unit (CTU, clinical trials unit) will perform the randomization and oversee the storage of the code list. CTU uses an independent printing house which prints and prepares envelopes with drug randomization inside. These opaque envelopes are then delivered to the study personnel at OUS.</i></p>
Study using Pre-Coded Randomization provided to site	<p><i>On the inclusion day (day of the surgery), after signing the informed consent, the participants will be assigned to one of the interventions accordingly to the randomization list, by study personnel.</i></p> <p><i>Each participant will be assigned a unique number (randomization number) in ascending numerical order, which encodes the participant's assignment to one of the arms of the study.</i></p> <p><i>A nurse or physician who is not part of the study team will open the sealed envelope and prepare the pre-surgery intervention.</i></p> <p><i>Each participant will be dispensed blinded study intervention, labelled with his/her unique randomization number, throughout the study.</i></p> <p><i>The medical staff involved in the administration of the intervention, and the pre and post-surgery questions (at baseline, pre- and post drug, see figure 2) will be blinded to the treatment assignment.</i></p>
Blind Break (Envelopes)	<p><i>A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the anaesthesia team. In case of an emergency, the anaesthetist has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor.</i></p>

Blinded study with unblinded site study personnel who is dispensing intervention	<p><i>Participants will be randomly assigned in a 1:1:1 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blinding, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. The study personnel will further ensure that all study medication is visually matched during the preparation. Only the participants number and no drug-specific code will be visible on the vial to the investigators to ensure allocation concealment across sessions.</i></p> <p><i>In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.</i></p>
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Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4. Study Intervention Compliance

The participants are dosed at the site, they will receive study intervention directly from the investigator (anaesthetist or study personnel), under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

Not applicable

6.5.1. Retreatment Criteria

Not applicable

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable

6.7. Treatment of Overdose

Interventions if SpO₂ < 90% for more than 3 minutes or immediately if SpO₂ < 85% or respiratory rate < 8:

- 1) Stimulate patient to achieve respiratory rate > 8 and/or deeper respiratory action.
- 2) Supplemental oxygen to 2 l/min.
- 3) Reversal agent: Naloxone® (naloxone) 0.1 mg IV. Repeated every 2-5 minutes until response.
- 4) Bag-mask ventilation and consider other reasons for hypoxemia than opioid effect.

6.8. Concomitant Therapy

Concomitant therapies would be treated according to the standard surgical procedures at Kongsberg Hospital and Oslo University Hospital. Analgesics, anti-inflammatory and anti-rheumatic drugs, antiepileptics and psychotropic medication (antipsychotic drugs, anxiolytics, sedatives and hypnotics, anti-depressants) must be recorded along with:

- 1) Reason for use
- 2) Dates of administration
- 3) Dosage information including dose and frequency

The Medical Monitor will be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Rescue Medicine

The study site will not supply rescue medication to patients. Possible rescue medicine (additional opioids, others) will be applied by the anaesthetic team immediately. After the anaesthesia induction, all patients will receive normal treatments according to the standard operation procedures of Kongsberg Hospital or Oslo University Hospital and the individual assessment.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

7.1.1. Liver Chemistry Stopping Criteria

Not applicable.

7.1.2. QTc Stopping Criteria

Not applicable.

7.1.3. Temporary Discontinuation

Not applicable.

7.1.4. Rechallenge

7.2. Participant Discontinuation/Withdrawal from the Study

1. A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
2. The participant will be permanently discontinued both from the study intervention and from the study at that time.
3. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow up

Not applicable.

7.4. Other safety procedures

The study is conducted in operation theatres. All the national and local standard operation procedures are followed. In detail, during application of the drug, an anaesthetist specialist and an anaesthetist nurse is conducting the anaesthesia procedure. In addition, an anaesthetist specialist or an anaesthetist nurse is conducting the study. In addition, an emergency team consisting of an additional anaesthetist specialist, an intensive nurse, an anaesthetist nurse, and an internal medicine specialist is available and on place within 5 minutes. Kongsberg hospital

and Oslo University Hospital have fully equipped intensive care units with possibilities for respiratory treatment and circulatory resuscitation.

All three medicaments are used daily in the hospitals and are registered several decades. Serious adverse effects (usually in higher dosages) include respiratory depression, and circulatory adverse effects, which are under control in this setting. As part of postoperative care, a standardized postoperative surveillance is used. An extremely rare serious adverse effect is an anaphylactic reaction. In this case, both the anaesthesia team, the study team and the emergency team are highly experienced to manage anaphylactic shock. In addition, patients are excluded who have a relevant history of anaphylactic reactions.

Minor adverse effects include dizziness, nausea, itch, and urine retention. These are typical adverse effects with a moderate incidence and would happen independent of the study. The standard operation procedures from Vestre Viken HF and Kongsberg hospital will be followed in this case, or similar standard procedures from Oslo University Hospital (OUS) for OUS sites.

Summarized will the study be conducted in a high security setting. It is highly unlikely that up to now unknown serious adverse effects will occur. Known possible serious adverse effects will be managed on specialist level and deleterious outcomes are highly unlikely. Minor adverse effects will be managed according to the standard operation procedures. All patients would in any case receive one of the three opioids, independent of the study.

8. Study Assessments and Procedures

4. Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
5. Immediate safety concerns will be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
6. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
7. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
8. Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

- Each patient is in the study period (after admission to the hospital day surgery unit until the anaesthesia conduction) under close observation of intensive care nurses, the study personnel and the anaesthesia team consisting of a senior anaesthetist and an anaesthetist nurse.
- Each patient will be monitored before the study drugs are applied with ECG, oxygen saturation and intermittent blood pressure (every 3rd minute) according to the standard operation procedure of Kongsberg hospital or Oslo University Hospital based on the Norwegian standard for anaesthesia.
- Postoperatively, patients will be monitored with ECG, oxygen saturation and intermittent blood pressure (every 5th to 10th minute) according to the standard operation procedure for postoperative treatment of Kongsberg hospital or Oslo University Hospital, again based on the Norwegian standard for anaesthesia.
- In addition, all Serious Adverse Events (SAEs) will be continuously monitored by the anaesthetists and the study personnel. The sponsors medical officer will review all SAEs and evaluate whether the event is expected according to the reference safety information (RSI). The Summary of Product Characteristics will be used as RSI in this trial. All SUSARs will be reported to the Norwegian Medical Agency within 7/15 days by the medical officer.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of a serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious.

Since all drugs are being used in several decades, and based on the advice of the Norwegian Medicines Agency, AEs will not be reported.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an SAE and remain responsible for following up.

The method of recording, evaluating, and assessing causality of SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention until the end of the study (when anaesthesia induction begins).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.2. Method of Detecting SAEs

Care will be taken not to introduce bias when detecting SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about SAE occurrences.

8.3.3. Follow-up of SAEs

After the initial SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, or the event is otherwise explained. Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs and SUSARs

9. Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

10. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
11. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB.
12. Suspected unexpected serious adverse reactions (SUSAR) will be reported through the EudraVigilance (EVCTM) system according to directive 2001/20/EC or regulation 536/2014 (<https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance>)
13. In addition, the sponsor will send every year a report according to the requirements of the Norwegian Medicines Agency ²

8.3.5. Pregnancy

Not relevant

8.3.6. Medical Device Deficiencies

Not applicable

²Rapportering for kliniske studier - Legemiddelverket

Doc. No. 2.01.1. Valid from March 2020.

Only the electronic version is valid.

9. Statistical Analysis Plan

SAP (and thereby also protocol) revision history:

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
AFFECT2 Version 2, 04.11.2022	1.0		Initial version. Not applicable.	
AFFECT2 Version 3 12.05.2026	2.0	1.1, table 1 in the protocol 3. same table as under 1.1 in the protocol SAP changed 9; 9.1-9.2-9.6	Added SAP revision history and an analysis plan for time of onset of drug effects. These changes were made after data collection was completed but prior to unblinding. Because of changes in the SAP table in section 1.1 and 3 (same table) in the protocol was changed	2026-05-12

The primary variables: Subjective drug effects, measured before and 2 minutes after intravenous administration across ten items (good, anxious, pain level, relaxed, dizzy, sedated, high, euphoric, drug liking, drug disliking) on 11-point numeric rating scales.

Secondary variables:

- Onset time of first subjective effect at 0-2 minutes and proportion who felt an effect
- Brief verbal descriptions of the effect experienced.
- Heart rate (beats-per-minute) from the ten minutes before and up to five minutes after drug administration.

9.1. Statistical Hypotheses

This RCT explores the subjective effects profiles of opioids commonly administered pre-surgery. Acute administration of opioids pre-surgery can produce positive and negative subjective effects that may or may not be beneficial. The quality and intensity of these subjective effects could depend on the opioid type and dose, as well as certain participant characteristics. The aim of the analysis plan for this RCT is therefore threefold:

We plan to write three separate papers with different outcomes collected in this trial:

Paper 1

Primary outcomes

- 1) To describe the subjective effects of morphine, oxycodone and fentanyl (each at three different doses: small, medium, and large) when administered pre-surgery.

Secondary outcomes

- 1) To determine the preferred treatment among morphine, oxycodone and fentanyl (each at three different doses: small, medium, and large), and placebo in terms of beneficial effects pre-surgery (i.e., feeling more relaxed, feeling less anxious, experiencing less pain, and feeling better).

Exploratory outcomes

- 2) Change in heart rate (HR) and heart rate variability (HRV) from before to after the drug administration
- 3) Correlation between self-reported drug effects
- 4) Correlation between self-reported drug high/intoxication and change in HR from before to after drug administration.

Paper 2

Primary outcomes:

- 1) Proportion of patients feeling an effect of the drug (yes/no) within 2 minutes of drug administration or saying yes to feeling an effect at 2 minutes.
- 2) Onset time of first subjective effect

Secondary outcomes:

- 3) Verbal report of the subjective drug experience, categorized
- 4) Adjusted onset time and proportion who felt an effect, when participants who said no to feeling an effect, but who rated 2 or higher on drug high and dizziness, are included.

Paper 3:

Primary outcomes:

- 1) To replicate and extend upon previous findings that prior opioid experience and affective state prior to surgery predict affective effects of opioids (e.g., feeling better or less anxious).

Secondary outcome:

- 2) Identify predictors of euphoria and drug liking in response to different opioids

9.2. Primary Analyses

9.2.1. Descriptions of Subjective and Physiological Effects

To describe the subjective and physiological effects of morphine, oxycodone, and fentanyl, we will plot dose-response curves for each of the 10 subjective effect measures (good, anxious, relaxed, pain, dizzy, sedated, high, euphoric, drug liking, drug disliking) and two physiological measures (heart rate and heart rate variability [RMSSD]) collected post treatment. The dose levels will be (in increasing order) placebo, small (2.5 mg morphine or oxycodone; 0.025 mg fentanyl), medium (5 mg morphine or oxycodone; 0.05 mg fentanyl), and large (10 mg morphine or oxycodone; 0.1 mg fentanyl). For measures that are collected both pre and post treatment administration (i.e., good, anxious, relaxed, pain level), scores observed

pretreatment will be included in the plots for reference. The dose-response curves will display the mean subjective rating or physiological level and corresponding 95% confidence interval at each dose level. To explore whether changes in subjective state coincide with changes in physiological state, we will also compute correlation coefficients between numeric changes in physiological measures from pre to post treatment and numeric changes in subjective effects measures from pre to post treatment. We will also specifically aim to replicate a significant association between intoxication levels and drug-related change in heart rate (post-pre) identified in our previous RCT.

9.2.2. Determining the Preferred Treatment

A common analytic approach to multi-arm RCTs is to conduct pairwise comparisons between treatment arms (Baron et al., 2013). However, ranking treatments based on pairwise comparisons becomes increasingly complex as more treatment arms and outcome measures are added to the study design (Juszczak et al., 2019). Fortunately, methods for ranking treatments have been developed in the context of network meta-analysis (Rücker & Schwarzer, 2015). These methods can generate treatment hierarchies based on a single or multiple outcome measures (Mavridis et al., 2020) and can easily be applied to multi-arm RCTs.

Network meta-analysis is a statistical method for combining data from individual studies into a connected network of multiple treatments of interest. This enables ranking of each treatment according to its estimated effect relative to all other treatments in the network. The 10 parallel treatment arms in this RCT form a network with 45 possible direct pairwise comparisons between treatment arms. To rank these treatments in terms of beneficial effects on subjective well-being, we will use an adaptation of network meta-analysis ranking methods. The analysis yields a ranking metric (P-score) per treatment, which can range from 0 (worst) to 1 (best) and reflects the average certainty that a particular treatment is superior to any of the other treatments in the network (Rücker & Schwarzer, 2015; Salanti et al., 2022). The treatment with the highest P-score is therefore considered the preferred treatment among the treatments in the network. P-scores account for both the magnitude and certainty of the difference in outcome between treatments. They can also be adjusted to account for numeric thresholds for clinical significance. Importantly, P-scores can be calculated to represent rankings on a single outcome measure or on multiple outcome measures (Mavridis et al., 2020). We will calculate a single multivariate P-score for each treatment arm based on the following four subjective effects measures: Anxious, relaxed, level of pain, and good. We will supplement this overall ranking metric with univariate P-scores per treatment arm calculated separately for each of these four measures. Additionally, we will calculate univariate P-scores per treatment arm for measures of other subjective effects that are less easily classified as desirable or undesirable in the preoperative context: Dizzy, sedated, high, euphoric, drug liking, and drug disliking. High ratings of drug high or euphoria (both >6) would be considered detrimental.

9.2.3. Time of onset

The current RCT was designed to accommodate assessment of the time of onset of subjective drug effects during the time interval between opioid administration and general anaesthesia. During the 2-minute waiting period immediately after drug administration, participants were instructed to report onset of subjective effects and the timing recorded. At 2 minutes, participants who had yet to report onset of subjective drug effects were explicitly asked if they felt any such effects (i.e., yes/no). Following the 2-minute waiting period and potential prompt, participants completed a brief questionnaire, including items

assessing their current feelings of being dizzy and intoxicated on 0-10 numeric rating scales (NRS). This design enables us to estimate the timing of subjective drug effects when these are reported either spontaneously, on prompt, or via NRS ratings.

Onset time data will be described in a separate paper than results on subjective and physiological effects and preferred treatment. This separation is to facilitate clarity given the large number of treatment arms and measured variables included in this large-scale trial.

Descriptive statistics for incidence (n and percentage) and onset time (mean, SD, median, IQR and range) per treatment arm will be computed for 1) the subset of participants who spontaneously reported feeling any drug effects within 2 minutes of drug administration, 2) the subset of participants who reported feeling such effects when explicitly asked at 2 minutes, and 3) the subset of participants who indicated feeling such effects through NRS ratings (i.e., dizzy and intoxicated ≥ 2). We will also provide the same descriptive statistics for the combination of subsets 1 and 2, and of subsets 1, 2 and 3. These descriptive statistics will be used to generate dose-response curves for onset time and reporting rate of subjective effects per opioid (morphine, oxycodone, and fentanyl), with the placebo arm serving as the reference condition.

Binary logistic regression will be used to model the probability of either spontaneously reporting feeling drug effects within 2 minutes or confirming feeling such effects at 2 minutes, as a function of treatment arm. We will also use binary logistic regression to model the probability of reporting feeling drug effects in any way (spontaneously, on prompt, or via NRS ratings) between drug administration and general anaesthesia, as a function of treatment arm. In both cases, we will conduct omnibus likelihood ratio (LR) χ^2 -tests to test for the presence of any differences in probabilities of feeling drug effects between treatment arms, as well as follow-up z-tests of differences in estimated marginal probabilities of feeling drug effects between pairs of treatment arms.

Next, we will analyze the onset time of these reports of subjective drug effects. The gamma distribution is a flexible distribution for modeling continuous non-zero positive outcome data with varying degrees of right-skewness, such as onset times. Gamma regression will therefore be used to model the onset time of subjective drug effects in this RCT as a function of treatment arm. In the first gamma regression model, we will model onset time as a function of treatment arm in the combined sample of participants who either spontaneously reported feeling drug effects within 2 minutes of drug administration or who reported feeling such effects when explicitly asked at 2 minutes. In a second gamma regression model, we will model onset time as a function of treatment arm in the total subset of participants who reported feeling drug effects in any way (i.e., spontaneously, on prompt, or via NRS ratings) between drug administration and general anaesthesia. Again, omnibus LR χ^2 -tests will be conducted to test for the presence of any differences in onset times between treatment arms, with follow-up z-tests to test for differences in estimated marginal mean onset times between pairs of treatment arms.

Based on prior literature describing analgesic onset time and pharmacokinetics of morphine, oxycodone, and fentanyl, we expect

1. Fastest onset time for fentanyl, followed by oxycodone and then morphine
2. Fastest onset time for large and slowest onset time for small doses

We will use z-tests for pairwise differences in onset times of subjective drug effects estimated from gamma regressions that model these timings as a function of drug type (morphine, oxycodone, fentanyl, and placebo) instead of treatment arm to test the hypothesis that onset times are faster for fentanyl, followed by oxycodone and then morphine (hypothesis 1). A similar approach replacing drug type with drug dose (none, low, medium, and high) will be used to test the hypothesis that onset times are fastest for large doses and slowest for small doses (hypothesis 2).

9.2.4. Predictors of Mood Improvements and positive drug effects: replication and extension

Results from a recent observational study conducted at Kongsberg Hospital indicate that prior opioid exposure and negative affect prior to surgery significantly predict mood improvements (i.e., feeling good) following administration of the opioids remifentanyl and oxycodone pre- surgery (Eikemo et al., 2023). To determine whether these findings replicate with the opioids used in this RCT, we will conduct ordinal logistic regressions similar to those reported in Eikemo et al. (2023). The outcome variables in these analyses will be changes in ratings of feeling good and anxious from pre to post treatment, recoded to an ordinal scale with the three levels “feeling worse” (≥ 1 point decrease), “feeling the same” (no change), and “feeling better” (≥ 1 point increase).

Main predictors of interest (i.e., prior opioid experience and negative affect prior to surgery) will be evaluated individually in separate analyses. Negative affect prior to surgery will be entered as a continuous predictor with a possible range of 0-10, based on affective state ratings before surgery. Negative affect in the week prior to surgery was measured using the HADS; separate scores for HADS depression and anxiety will be used. Prior opioid experience will be entered as a categorical predictor with the three levels “opioid naïve” (i.e., no prior opioid use), “some experience” (i.e., prior opioid use lasting ≤ 2 weeks), and “prolonged use” (i.e., prior opioid use lasting > 2 weeks). Participants who did not disclose information about prior opioid use will be excluded from this analysis. The models will include treatment, sex, and age as covariates. The replication analyses will only include the opioid arms of the RCT. We will also conduct various sensitivity analyses and exploratory analyses. Because the doses used in this RCT are fixed, we will run models with weight as an additional predictor to assess whether participants’ weight contributes to variation in mood improvements with opioids. We will also run models that allow for interaction between treatment and the main predictor of interest. These models will include the placebo arm and will address whether the effect of prior opioid use or negative affect on mood improvement following treatment administration differs between treatment drugs.

The statistical significance of marginal main and interaction effects in these models will be assessed with likelihood ratio chi-squared ($LR \chi^2$) tests.

Additional analyses will use a multimodel inference approach to identify the most important measured predictors of subjective effects of different opioids.

9.3. Demographic and Baseline Variables

Summary statistics for a range of demographic and baseline variables (e.g., health status, surgical procedures, resting heart rate, prior and concomitant medications, age, gender, and pain measures) will be produced. Continuous variables will be summarized using the following descriptive statistics: *n* (non-missing sample size), *mean*, *standard deviation*, *median*, *maximum*, and *minimum* where relevant. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

9.4. Missing Data

For the primary outcomes, a table or graph showing the percentage of missing data will be produced. We

assume little drop-out and missing data based on implementing a similar procedure in more than 200 participants in a quality assurance study (Eikemo et al., 2023). Missing data will be handled by means of pairwise deletion to minimize data loss across analyses.

9.5. Sample Size Determination

The expected sample size for this RCT was determined primarily by logistical factors. The sample in this RCT is a convenience sample and the final sample size depends on the recruitment and testing capacity at each of the two study sites throughout the duration of the RCT. Based on pilot data and experience from a recent quality control study (Eikemo et al., 2023), we expect to enroll 800-1000 participants in total. We conducted power analyses to assess the minimum effect size we would likely be able to detect with the planned analyses and expected sample size. These calculations were done in *R* (R Core Team, 2024) and used an unadjusted alpha level of 0.05. With approximately 80 participants in each treatment arm, power analysis with the function *pwr.t2n.test* from the *pwr* package (Champely, 2020) indicates that we would have 90% power to detect a Cohen's *d* of 0.52 in pairwise comparisons (*t*-tests) between treatment arms. Power analysis for ordinal logistic regressions were implemented using the function *popower* from the *Hmisc* package (Harrell Jr, 2021). These calculations were based on frequencies of opioid use and anxiety as well as estimated marginal probabilities of mood improvements in a previous observational study (Eikemo et al., 2023). With approximately 720 participants receiving an opioid drug, we would have 90% power to detect 1.59-2.03 times greater odds of ≥ 1 point mood improvement (i.e., increase in feeling good or decrease in feeling anxious) for participants with more relative to less prior opioid experience or negative affect.

9.6. Multiple Testing

This RCT combines hypothesis testing with an exploratory approach. Corrections for multiple testing will only be applied in analyses evaluating the replicability of results from exploratory analyses in a previous observational study (Eikemo et al., 2023). This set of analyses consists of three *LR* χ^2 tests of interest. These tests assess the statistical significance of the marginal main effects of 1) prior opioid experience on change in feeling good, 2) prior negative affect on change in feeling good, and 3) prior negative affect on change in feeling anxious. The tests will be grouped into families according to the outcome variable (i.e., change in feeling good and change in feeling anxious) and Bonferroni correction will be applied within each family. As such, the adjusted alpha levels for significant predictors in analyses of change in feeling good and change in feeling anxious will be 0.025 ($k = 2$) and 0.05 ($k = 1$), respectively.

9.7. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

<i>Participant Analysis Set</i>	<i>Description</i>
<i>Randomized</i>	<i>All participants allocated to the randomization list after informed consent</i>
<i>Evaluable</i>	<i>All participants with at least one item on baseline and pre/post drug</i>

<i>Safety</i>	<i>All randomized participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received. The statistician conducting the analysis will be blinded to the study manipulation.</i>
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<i>Defined Analysis Data Sets</i>	<i>Description</i>
<i>Analysis set for primary estimand</i>	<i>All randomized participants. Participants who discontinue study intervention are included up to the point of discontinuation, unless they withdraw their consent for already collected data points.</i>
<i>Analysis for secondary parameters</i>	<i>All randomized participants. Participants who discontinue study intervention are included up to the point of discontinuation, unless they withdraw their consent for already collected data points.</i>

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

14. This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations
15. The protocol, protocol amendments, ICF, SmPC, questionnaires and other relevant documents are submitted to an IRB/IEC by the investigator and reviewed and will be approved by the IRB/IEC before the study is initiated.
16. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
17. Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
18. The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

19. The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

20. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

21. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
22. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
23. A copy of the ICF(s) must be provided to the participant.

10.1.4. Data Protection

24. Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
25. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
26. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Study monitoring will be based on the risk assessment and will be performed by Forskningsenheten at Vestre Viken Trust for Kongsberg and Oslo University Hospital sites.

10.1.6. Dissemination of Clinical Study Data

10.1.7. Data Quality Assurance

27. All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
28. Guidance on completion of CRFs will be provided in a standard operation procedure provided to the study personnel.
29. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
30. Quality tolerance limits (QTLs) will be pre-defined in the monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

31. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
32. The sponsor is responsible for the data management of this study including quality checking of the data.
33. Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for five years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

34. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
35. Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
36. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
37. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study Termination

The sponsor reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.

10.1.10. Publication Policy

- 38. The results of this study may be published or presented at scientific meetings
- 39. The sponsor will comply with the requirements for publication of study results.
- 40. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- Not applicable.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

Note that AEs will not be registered in this study. The definition of AE is added to make the distinction to SAEs and SUSAR clear.

AE Definition
<p>41. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.</p> <p>42. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.</p>
Definition of Unsolicited and Solicited AE
<p>43. An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.</p> <p>44. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participants concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records..</p>

Events Meeting the AE Definition
<p>45. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).</p> <p>46. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</p>

47. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
48. Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
49. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
50. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

51. Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
52. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
53. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
54. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
55. Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

A SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

56. In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

<p>outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.</p> <p>57. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.</p>
<p>d. Results in persistent or significant disability/incapacity</p> <p>58. The term disability means a substantial disruption of a person’s ability to conduct normal life functions.</p> <p>59. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.</p>
<p>e. Is a congenital anomaly/birth defect</p>
<p>f. Is a suspected transmission of any infectious agent via an authorised medicinal product]</p>
<p>g. Other situations:</p> <p>60. Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.</p> <p>s of such events include invasive or malignant cancers, intensive treatment for allergic spasm, blood dyscrasias, convulsions or development of intervention dependency or on abuse.</p>

10.3.3. Definition of SUSAR (suspected unexpected serious adverse reaction)

A SUSAR is defined as any serious adverse event that, at any dose:
<p>a. Results in death</p>
<p>b. Is life-threatening</p> <p>The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.</p>

c. Requires inpatient hospitalization or prolongation of existing hospitalization

61. In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
62. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

63. The term disability means a substantial disruption of a person's ability to conduct normal life functions.
64. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- f.** Is a suspected transmission of any infectious agent via an authorised medicinal product]

g. Other situations:

65. Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- s of such events include invasive or malignant cancers, intensive treatment for allergic spasm, blood dyscrasias, convulsions or development of intervention dependency or on abuse.

10.3.4. Recording and Follow-UP of SAE and SUSAR

SAE and SUSAR Recording

1. When a SAE or SUSAR occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

<ol style="list-style-type: none"> The investigator will then record all relevant SAE or SUSAR information. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the SAE or SUSAR.
Assessment of Causality
<ol style="list-style-type: none"> The investigator is obligated to assess the relationship between study intervention and each occurrence of each SAE/SUSAR. A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. For each SAE or SUSAR, the investigator must document in the medical notes that he/she has reviewed the SAE and has provided an assessment of causality. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE or SUSAR follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of SAEs and SUSARs
<ol style="list-style-type: none"> The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the SAE or SUSAR as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the originally submitted documents.

10.3.5. Reporting of SAEs

SAE Reporting to the sponsor and study monitor via Paper Data Collection Tool
<ol style="list-style-type: none"> Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor and study monitor

10.3.6. Reporting of SUSARs

SUSAR Reporting to the sponsor and study monitor via Paper Data Collection Tool

The initial SUSAR report must contain at least the following information:

4. Valid EudraCT number
5. Sponsor study number, (e.g. REK reference number)
6. One identifiable coded subject
7. One identifiable reporter
8. One SUSAR
9. One suspect IMP

The initial SUSAR report should contain in addition:

- A full description of the event (or if all the information is not available at the time of the initial report, this could be included in the follow-up), including the event start date, whether or not it is resolved and, if resolved, the date of resolution
- Any relevant medical history or relevant concurrent conditions that are not already listed as part of the
- event
- An assessment of seriousness and expectedness
- Dates that the suspected drug was administered to the subject, and whether any changes to
- administration have been made as a result of the event (such as ceasing the medication, or changing the dose)
- Details of any concomitant medications
- In the case of death, the date and cause of death
- Receipt date of the information from the investigator
- Whether the report is an initial report or a follow-up report

10. The first report has to be submitted within 7 days

11. The Follow-Up report has to be issued within 15 days.

12. Facsimile transmission of the SAE/SUSAR paper data collection tool is the preferred method to transmit this information to the sponsor, study monitor, and authorities.

13. The authorities to be reported are the Norwegian Board of Health Supervision (Statens helsetilsyn) and the Norwegian Medicines Agency (Statens legemiddelverk).

Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [amendment number]:

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale

11. References

- Angst, M. S., Lazzeroni, L. C., Phillips, N. G., Drover, D. R., Tingle, M., Ray, A., . . . Clark, J. D. (2012). Aversive and reinforcing opioid effects: a pharmacogenomic twin study. *Anesthesiology*, 117(1), 22-37. doi:10.1097/ALN.0b013e31825a2a4e
- Astuto, M., & Lauretta, D. (2009). Anesthesia Induction. In M. Astuto (Ed.), *Basics* (pp. 85-99). Milano: Springer Milan.
- Baron, G., Perrodeau, E., Boutron, I., & Ravaud, P. (2013). Reporting of analyses from randomized controlled trials with multiple arms: a systematic review. *BMC Medicine*, 11(1), 84. doi:10.1186/1741-7015-11-84
- Bershad, A. K., Miller, M. A., Norman, G. J., & de Wit, H. (2018). Effects of opioid- and non-opioid analgesics on responses to psychosocial stress in humans. *Horm Behav*, 102, 41-47. doi:10.1016/j.yhbeh.2018.04.009
- Bjerkeset, O., Romild, U., Smith, G. D., & Hveem, K. (2011). The associations of high levels of C-reactive protein with depression and myocardial infarction in 9258 women and men from the HUNT population study. *Psychol Med*, 41(2), 345-352. doi:10.1017/s0033291710000887
- Champely, S. (2020). pwr: Basic Functions for Power Analysis (Version 1.3-0).
- Choudhary, P., Dutta, A., Sethi, N., Sood, J., Rai, D., & Gupta, M. (2019). Pre-induction fentanyl dose-finding study for controlled hypotension during functional endoscopic sinus surgery. *Indian J Anaesth*, 63(8), 653-659. doi:10.4103/ija.IJA_866_18
- Colasanti, A., Rabiner, E. A., Lingford-Hughes, A., & Nutt, D. J. (2011). Opioids and anxiety. *J Psychopharmacol*, 25(11), 1415-1433. doi:10.1177/0269881110367726
- Courtwright, D. T. (2001). *Dark Paradise: A History of Opiate Addiction in America*. Cambridge MA: Harvard University Press.
- Dale, O., Moksnes, K., & Kaasa, S. (2011). European Palliative Care Research Collaborative pain guidelines: Opioid switching to improve analgesia or reduce side effects. A systematic review. *Palliat Med*, 25(5), 494-503. doi:10.1177/0269216310384902
- Deighton, S., Neville, A., Pusch, D., & Dobson, K. (2018). Biomarkers of adverse childhood experiences: A scoping review. *Psychiatry Res*, 269, 719-732. doi:10.1016/j.psychres.2018.08.097
- Doleman, B., Leonardi-Bee, J., Heinink, T. P., Bhattacharjee, D., Lund, J. N., & Williams, J. P. (2018). Pre-emptive and preventive opioids for postoperative pain in adults undergoing all types of surgery. *Cochrane Database Syst Rev*, 12, Cd012624. doi:10.1002/14651858.CD012624.pub2
- Drewes, A. M., Jensen, R. D., Nielsen, L. M., Droney, J., Christrup, L. L., Arendt-Nielsen, L., . . . Dahan, A. (2013). Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br J Clin Pharmacol*, 75(1), 60-78. doi:10.1111/j.1365-2125.2012.04317.x

- Dutta, A., Sethi, N., Choudhary, P., Sood, J., Panday, B. C., & Chugh, P. T. (2018). The impact of preinduction fentanyl dosing strategy on postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. *J Opioid Manag*, 14(4), 283-293. doi:10.5055/jom.2018.0460
- Eikemo, M., Meier, I. M., Løseth, G. E., Trøstheim, M., Ørstavik, N., Jensen, E. N., . . . Leknes, S. (2022). Do opioid analgesics improve subjective well-being? A prospective observational study of acute opioid effects before surgery. *PsyArXiv Preprints*. doi:10.31234/osf.io/pq7dh
- Evans, S. M., Foltin, R. W., Levin, F. R., & Fischman, M. W. (1995). Behavioral and subjective effects of DN-2327 (pazinaclone) and aiprazolam in normal volunteers. *Behav Pharmacol*, 6(2), 176-186. doi:10.1097/00008877-199503000-00010
- Garland, E. L., Froeliger, B., Zeidan, F., Partin, K., & Howard, M. O. (2013). The downward spiral of chronic pain, prescription opioid misuse, and addiction: cognitive, affective, and neuropsychopharmacologic pathways. *Neurosci Biobehav Rev*, 37(10 Pt 2), 2597-2607. doi:10.1016/j.neubiorev.2013.08.006
- Harrell Jr, F. E. (2021). Hmisc: Harrell Miscellaneous (Version 4.5-0).
- Helsedirektoratet. (2018). *Utvikling og variasjon i kirurgisk behandling 2013-2017*. Retrieved from Oslo:
- Inglis, L. (2018). *Milk of paradise : a history of opium*. London: Macmillan.
- Juszczak, E., Altman, D. G., Hopewell, S., & Schulz, K. (2019). Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA*, 321(16), 1610-1620. doi:10.1001/jama.2019.3087
- Li, P. H., Ue, K. L., Wagner, A., Rutkowski, R., & Rutkowski, K. (2017). Opioid Hypersensitivity: Predictors of Allergy and Role of Drug Provocation Testing. *J Allergy Clin Immunol Pract*, 5(6), 1601-1606. doi:10.1016/j.jaip.2017.03.035
- Martel, M. O., Dolman, A. J., Edwards, R. R., Jamison, R. N., & Wasan, A. D. (2014). The association between negative affect and prescription opioid misuse in patients with chronic pain: the mediating role of opioid craving. *J Pain*, 15(1), 90-100. doi:10.1016/j.jpain.2013.09.014
- Mavridis, D., Porcher, R., Nikolakopoulou, A., Salanti, G., & Ravaud, P. (2020). Extensions of the probabilistic ranking metrics of competing treatments in network meta-analysis to reflect clinically important relative differences on many outcomes. *Biometrical Journal*, 62(2), 375-385. doi:10.1002/bimj.201900026
- McHugh, R. K., Weiss, R. D., Cornelius, M., Martel, M. O., Jamison, R. N., & Edwards, R. R. (2016). Distress Intolerance and Prescription Opioid Misuse Among Patients With Chronic Pain. *J Pain*, 17(7), 806-814. doi:10.1016/j.jpain.2016.03.004
- Morean, M. E., de Wit, H., King, A. C., Sofuoglu, M., Rueger, S. Y., & O'Malley, S. S. (2013). The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology (Berl)*, 227(1), 177-192. doi:10.1007/s00213-012-2954-z

- Natusch, D. (2012). Equianalgesic doses of opioids - their use in clinical practice. *Br J Pain*, 6(1), 43-46. doi:10.1177/2049463712437628
- Naude, P. J. W., Roest, A. M., Stein, D. J., de Jonge, P., & Doornbos, B. (2018). Anxiety disorders and CRP in a population cohort study with 54,326 participants: The LifeLines study. *World J Biol Psychiatry*, 19(6), 461-470. doi:10.1080/15622975.2018.1433325
- R Core Team. (2021). R: A language and environment for statistical computing. (Version 4.1.1). Vienna, Austria: R Foundation for Statistical Computing.
- Rücker, G., & Schwarzer, G. (2015). Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology*, 15(1), 58. doi:10.1186/s12874-015-0060-8
- Salanti, G., Nikolakopoulou, A., Efthimiou, O., Mavridis, D., Egger, M., & White, I. R. (2022). Introducing the Treatment Hierarchy Question in Network Meta-Analysis. *American Journal of Epidemiology*, 191(5), 930-938. doi:10.1093/aje/kwab278
- Schaffer, C. B., Nordahl, T. E., Schaffer, L. C., & Howe, J. (2007). Mood-Elevating Effects of Opioid Analgesics in Patients With Bipolar Disorder. *J Neuropsychiatry Clin Neurosci*, 19(4), 449-452. doi:10.1176/jnp.2007.19.4.449
- Sgoifo, A., Carnevali, L., Alfonso Mde, L., & Amore, M. (2015). Autonomic dysfunction and heart rate variability in depression. *Stress*, 18(3), 343-352. doi:10.3109/10253890.2015.1045868
- Sneider, W. (2005). *Drug discovery : a history*. Chichester: Wiley.
- Stanley, T. H. (1992). The history and development of the fentanyl series. *J Pain Symptom Manage*, 7(3 Suppl), S3-7. doi:10.1016/0885-3924(92)90047-1
- Stone, A. L., Becker, L. G., Huber, A. M., & Catalano, R. F. (2012a). Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addictive Behaviors*. doi:S0306-4603(12)00081-0 [pii] 10.1016/j.addbeh.2012.02.014
- Stone, A. L., Becker, L. G., Huber, A. M., & Catalano, R. F. (2012b). Review of risk and protective factors of substance use and problem use in emerging adulthood. *Addict Behav*, 37(7), 747-775. doi:10.1016/j.addbeh.2012.02.014
- Thomas, E. A., & Garland, E. L. (2017). Mindfulness is Associated With Increased Hedonic Capacity Among Chronic Pain Patients Receiving Extended Opioid Pharmacotherapy. *Clin J Pain*, 33(2), 166-173. doi:10.1097/ajp.0000000000000379
- Tracey, I., Woolf, C. J., & Andrews, N. A. (2019). Composite Pain Biomarker Signatures for Objective Assessment and Effective Treatment. *Neuron*, 101(5), 783-800. doi:10.1016/j.neuron.2019.02.019
- Wang, L. P., Hermann, C., & Westrin, P. (1996). Thiopentone requirements in adults after varying pre-induction doses of fentanyl. *Anaesthesia*, 51(9), 831-835. doi:10.1111/j.1365-2044.1996.tb12611.x